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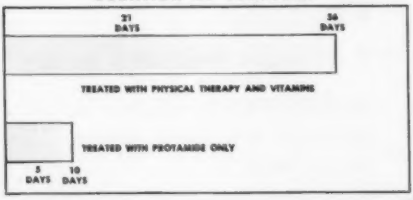

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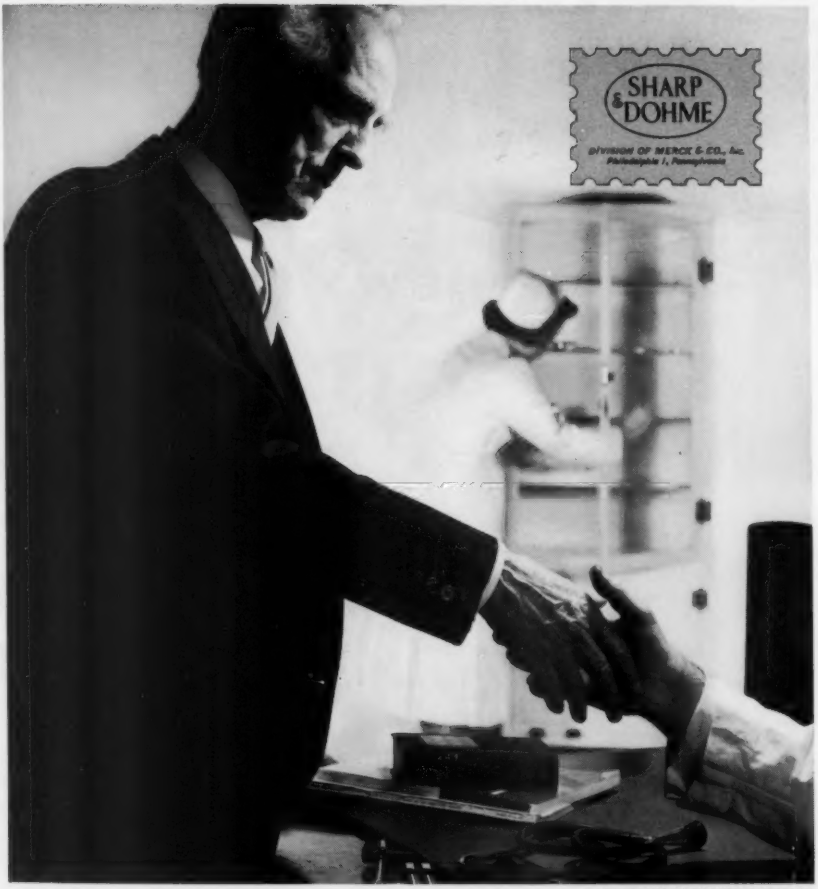

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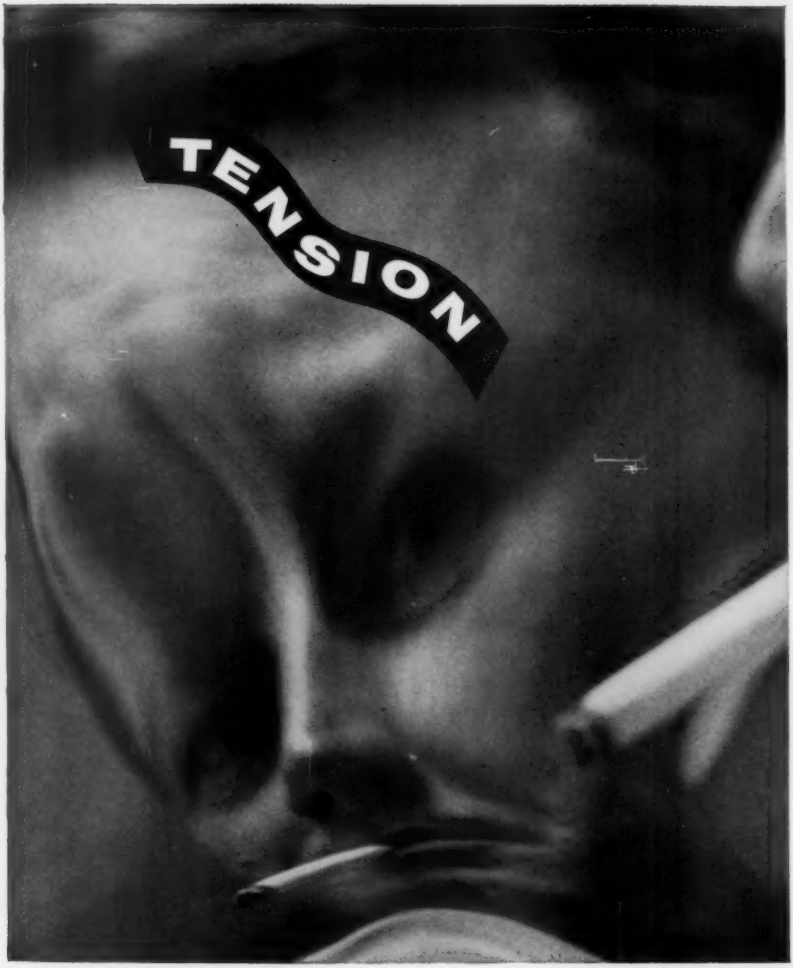

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NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

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The Perspective of Neurology in Regard to Polymyositis

A Study of 41 Cases

Lee M. Eaton, M.D

THROUGH several years in the neurologic sections of the Mayo Clinic we have encountered cases which have resembled one another in certain features. Yet they have defied accurate diagnostic classification. These cases have been characterized by relatively rapid development of symmetric weakness, chiefly of the proximal muscles of the extremities. Our frustration led us to adopt diagnostic aids not generally used. Of these, more later; the data obtained have been correlated and the clinical entity, polymyositis, is now being recognized with increasing frequency. The importance of this lies in the clinical impression, not yet proved, that treatment with cortisone is of value.

"Polymyositis" is a term distinguished by the ambiguity which surrounds its use. In the past it has had at least two meanings. At present it seems to be developing another. In the narrowest sense, "polymyositis" has been descriptive of specific alterations in the histologic picture of muscle. More broadly, the term has been taken in preference to "dermatomyositis," provided the cutaneous lesions which characterize the latter illness were absent. Finally, it seems to me that "polymyositis" may prove to be the most appropriate term to designate the similar muscular component which is found in a group of related but dissimilar disorders, the so-called collagen diseases.

From the section of neurology, Mayo Clinic, Rochester, Minnesota.

Presidential address read at the Central Neuropsychiatric Association meeting, Indianapolis, Indiana, October 16, 1953.

The perspective of the neurologist has been important to the development of the present concept of polymyositis. Perhaps more than any other diagnostician, the neurologist is accustomed to recognize muscular weakness or dysfunction resulting from disease of the nervous system; he becomes adept in the diagnosis of muscular dystrophy and myasthenia gravis. But in a case which has the superficial characteristics of muscular dystrophy there may also be features which require that the case be placed in the category of dermatomyositis. These features are cutaneous lesions and constitutional symptoms.

As the years pass, the neurologist becomes aware that in patients whom he is seeing repeatedly, although infrequently, there is a resemblance to muscular dystrophy except that the illness has developed too rapidly and often too late in life. The tempo of evolution of the weakness suggests diseases of the anterior horn cells, such as amyotrophic lateral sclerosis. However, the process is localized too symmetrically to the proximal muscles, and fasciculations usually are lacking. Although the resemblance to myasthenia gravis is striking, particularly when dysphagia and facial weakness are prominent, the neurologist can neither combat the weakness by administration of neostigmine nor exaggerate it by giving small doses of curare. At times he considers neuronitis (Guillain-Barré syndrome), but albuminocytologic dissociation is not evident on examination of the cerebrospinal fluid and the course of the illness is not characteristic of neuronitis. He may resort to the counterfeit label, "atypical muscular dystrophy."

In my own work, hints as to the true nature of the illness arose in study of individual cases. In 1944 I encountered a patient with a basal metabolic rate of +36 per cent (case 24 in table 1). Colleagues in metabolism were sure that the patient was euthyroid. Thus was born an interest in the basal metabolic rates of patients with muscular weakness. Occasionally, elevation of the sedimentation rate or some change in the constituents of the blood aroused the suspicion that muscular weakness was the result of a constitutional disease. In 1948 a patient (case 34) was examined whose condition would have been classified by me as atypical muscular dystrophy except for an accident: exposure to the sun's rays for 20 minutes produced edema and erythema of the skin, which were considered by colleagues in dermatology to be diagnostic of dermatomyositis. I began to wonder if the muscular troubles of the patients whose condition I was unable to diagnose were the same as those of the patients who had dermatomyositis.

In 1946 development of the laboratory of electromyography had been begun by Dr. E. H. Lambert. Soon he detected similar electromyographic abnormalities in classic cases of dermatomyositis and in the perplexing cases mentioned.[1]

Another impetus to recognition of the similarities between dermatomyositis and what was being called atypical muscular dystrophy was brought about by a decision of my neurologic colleagues and me again to pry into the value of muscle biopsy. At the time, we were using muscular biopsy only sporadically because it had been of small help to us. However, Dr. C. J. Chen

devoted the year 1948 to this segment of the investigation, under the direction of Dr. George Sayre. The study continues under Dr. Sayre's direction and the increasing use of muscular biopsy is coincident with its augmented diagnostic value.

Weekly conferences on neuromuscular disorders begun in 1951 have furnished invaluable correlation of clinical, histologic, and electromyographic observations on which progress toward understanding depends.

DERMATOLOGIC BACKGROUND

The concept of polymyositis which is emerging from study of cases reported in this paper can be viewed against the background of the clinical picture of dermatomyositis and the related diseases, scleroderma and acrosclerosis. The syndromes of disseminated lupus erythematosus and periarteritis nodosa also might be reviewed with profit, but these entities are more generally understood than are the others and will be omitted here. Background information has been drawn from the writings of O'Leary and certain of his co-authors, from Brock,[2–6] and from information gained from discussion of cases with Brunsting, Montgomery, and Kierland.

Scleroderma and acrosclerosis. These can be quickly discussed. Scleroderma and acrosclerosis occur more commonly than dermatomyositis, and are seen most frequently in women between 30 and 50 years of age.

Localized forms of scleroderma are of three types: 1) morphea, or localized patches of scleroderma, 2) linear scleroderma, or localized streaks, and 3) sclerodactylia, or changes in the hands which result in hidebound, tapered fingers and bowed nails. In the severest cases, gangrenous ulceration may be an associated finding. Diffuse scleroderma most often begins gradually, with painless, brawny, swelling of the neck, face, arms, and trunk. Raynaud's phenomena occur in many cases but seldom precede onset of the sclerosing process.

Acrosclerosis is the diagnosis reserved for cases of Raynaud's disease in which scleroderma affects the distal portions of the extremities, the face, and the neck. Raynaud's phenomena usually appear first in the fingers and precede the sclerodactylia by a month or more. Sclerosing changes may occur simultaneously or later in the face and over the shoulder girdle and chest. When the face is involved the mouth appears small, the patient cannot open it wide, and the nose appears pinched. The forearms and lower extremities are involved infrequently.

According to Olsen, O'Leary, and Kirklin,[6] approximately 10 per cent of patients who have scleroderma and acrosclerosis complain of dysphagia. When the esophagus is involved, roentgenologic examination often discloses that it is dilated, atonic, and occasionally obstructed at the cardia by spasm. The esophagus may be shortened sufficiently that the stomach is drawn through the esophageal hiatus into the thorax. On endoscopic examination, the gastric mucosa is pale, smooth, thickened, and occasionally ulcerated.

The course of scleroderma and of acrosclerosis is protracted. Spontaneous

remissions occur and progress is arrested in approximately 25 per cent of cases. Approximately 10 per cent of patients die. O'Leary[3] stated that involvement of muscle, which is an outstanding feature of dermatomyositis, appears late in scleroderma and in acrosclerosis, while pigmentation of the skin and deposition of calcium in the skin, underlying tissue, and muscles may appear in all.

Dermatomyositis. Dermatomyositis is rare; it affects children and adults of both sexes. It may begin abruptly or subacutely. The symptoms, for convenience of description, may be grouped as those resulting from systemic, cutaneous, or muscular involvement.

The systemic symptoms are variable and tend not to be prostrating. They include fever, loss of weight, and tachycardia. Lymphadenopathy, splenomegaly, leukocytosis, and eosinophilia occasionally are present but usually are not pronounced. More commonly the sedimentation rate is increased. Anemia is not a feature. Vasospastic changes such as are manifest in Raynaud's phenomenon may occur, and in some cases arthritis and arthralgia are associated. Elevation of the basal metabolic rate has been observed by our dermatologists and by others[7] but, since they have found this rate elevated in other so-called collagen diseases, it has not aided them significantly in differential diagnosis. Dermatomyositis is too frequently an accompaniment of malignancy to justify attributing the association to coincidence.

The dermatologic manifestations may be entirely lacking and anyway they are variable. In the majority of recognized cases, however, they are sufficiently characteristic that, when associated with grossly recognizable muscular weakness, the diagnosis is not difficult, at least to the experienced dermatologist. Inflammatory edema about the eyes and on the face and extremities is of common occurrence and, on rare occasions, it may be generalized. Erythema, at times with a violaceous tint (heliotrope), diffuse or mottled and not limited to the edematous areas, is of common occurrence. At times, however, only the heliotrope coloring is present to suggest the diagnosis of dermatomyositis. Eruptive, pigmentary, and atrophic changes in sharply demarcated patches, particularly over the knuckles and backs of the hands and over the face, neck, sternum, elbows, and knees, are frequently observed. Sclerosis of the skin and underlying tissues tends to occur late and is not a regular feature of this disease as it is of scleroderma and acrosclerosis. However, when sclerosis is unusually prominent and the patient is seen in the chronic stage of the disease, differential diagnosis from scleroderma and acrosclerosis may be difficult. Alopecia, stomatitis, and calcification of the skin, subcutaneous tissue, and muscles may be observed.

The most prominent symptom of muscular involvement is weakness which tends to be symmetric and to involve the neck, shoulder, and pelvic girdle. Often the muscles are painful, sore, and to the examiner they may feel hard and swollen. Loss of reflexes, atrophy, and contractures tend to appear late. Occasionally the cardiac muscle, muscles of respiration, muscles of the face and eyes, and the sphincters are involved. Dysphagia occurs in more than

half of the cases but it is not always clear whether it results from weakness of the musculature or from muscular dysfunction secondary to inflammatory and edematous changes in the mucosa and submucosa.

The mortality of dermatomyositis is high. Brock[5] found that in 40 of 75 reported cases the patients had died and that 55 per cent of the deaths had occurred within two years of onset. Of 38 patients followed by O'Leary and Waisman,[2] 19 had died; the average duration of the disease at death was two years; the range, four months to six years. On the other hand, four of 38 patients had completely recovered and the diseases of seven had become stationary.

My colleagues in dermatology have learned from their own experience and from reports in the literature that dermatomyositis may occur without cutaneous manifestations.

Steiner,[8] who in 1904 described a case of dermatomyositis that was studied on Osler's service at Johns Hopkins, was apparently the first to report on this disease in the American literature. He pointed out that inflammatory changes in muscles had "long been recognized" and that they might occur in association with other diseases or independently. According to Steiner, the first descriptions of dermatomyositis appeared in the literature almost simultaneously in 1887, under the authorship, respectively, of E. Wagner, Hepp, and Unverricht. To the last was given the credit for coining the descriptive term "dermatomyositis." Steiner reviewed the reports of cases published previously, in one of which there were no significant cutaneous lesions.

Brock,[5] writing on dermatomyositis and diffuse scleroderma, called attention to the fact that in literature the terms "dermatomyositis" and "polymyositis" had been used interchangeably. He stated that, according to his conception, the term "dermatomyositis" denoted the combination of polymyositis and inflammation of the skin. O'Leary[4] stated, "In an occasional patient cutaneous lesions may be entirely lacking, in which case 'polymyositis' is the term that describes the entity more accurately than dermatomyositis. In fact, it is well to think of dermatomyositis as polymyositis with variable cutaneous lesions."

How then, since polymyositis (dermatomyositis without cutaneous lesions) has been known for many years, did it happen that the neurologist failed to recognize many cases of polymyositis without skin lesions? I believe three factors are accountable: 1) Oscillographic electromyography has been available for only a few years and electromyographers in general have not had sufficient experience with polymyositis or dermatomyositis to become aware of the characteristic electromyographic abnormalities produced by these disorders. 2) Biopsy of muscle, except in a few institutions, has not been persisted in, and correlated with, enough well-studied cases to develop into a reliable diagnostic aid. 3) Finally, lacking these two diagnostic aids it has not been generally recognized that polymyositis may be unattended by muscular pain and tenderness or by profound constitutional symptoms. In other

words, the clinical picture was not seen with sufficient clarity and the most important laboratory aids to diagnosis were not utilized or were not available.

HISTOLOGIC AND ELECTROMYOGRAPHIC ABNORMALITIES

For clarity, it will be advisable to delay discussion of the clinical studies until the histologic and electromyographic observations in the disease under consideration have been described.

Histologic Abnormalities in Polymyositis

In polymyositis various alterations in the histologic appearance of muscle have been encountered (figure 1). Changes confined to the muscle fibers which may be classed as degenerative and proliferative are regularly observed. Unfortunately, in the present state of knowledge, these changes are not in themselves diagnostic; similar alterations are found in cases of classic muscular dystrophy and in diseases which produce denervation of muscle. The inflammatory changes in the interstitial tissue (interstitial myositis), although not always found in a single specimen taken for biopsy, are of greater diagnostic reliability when present.

The extent of the degenerative changes observed in the muscle fibers parallels remarkably the extent to which the muscle is involved clinically. In severely weakened muscles, severe sarcoplasmic degeneration may be observed in the great majority of fibers. In stronger muscles, sarcoplasmic degeneration may be found in only a few fibers and, in them, the changes may appear to be limited to segments of the fibers.

Sarcoplasmic degeneration. The earliest sarcoplasmic changes appear to be alterations in staining. Certain fibers, or only segments of fibers, stain homogeneously with eosin or occasionally display an affinity for hematoxylin. At this stage the striations are not readily seen and the fibers or segments of fibers may become greatly swollen. Later, clear vacuoles or lakes appear, often in the neighborhood of enlarged muscle nuclei which have migrated into the sarcoplasm. In areas in which degeneration is severe, phagocytic cells may be observed within the fibers and also in the neighboring endomysium. Eventually, the sarcoplasm may undergo complete dissolution, leaving tubes of fiber membranes containing only an increased number of nuclei.

Proliferative nuclear changes. Perhaps the earliest changes in the muscle fibers are of proliferative type. The nuclei of the muscle fibers, which normally are elongated and lie beneath the sarcolemma, become rounded and enlarged so that the nucleoli are easily seen. The nuclei increase in number, often forming columns which resemble chains of beads. At times the nuclei are in clusters. Relatively early the nuclei are centrally located in the muscle fibers, having migrated from their normal position beneath the sarcolemma.

Interstitial myositis. The interstitial inflammatory changes may precede all other changes (case 12). Although interstitial myositis always may be present in cases of polymyositis, it is not always observed in the portion of muscle removed at biopsy.

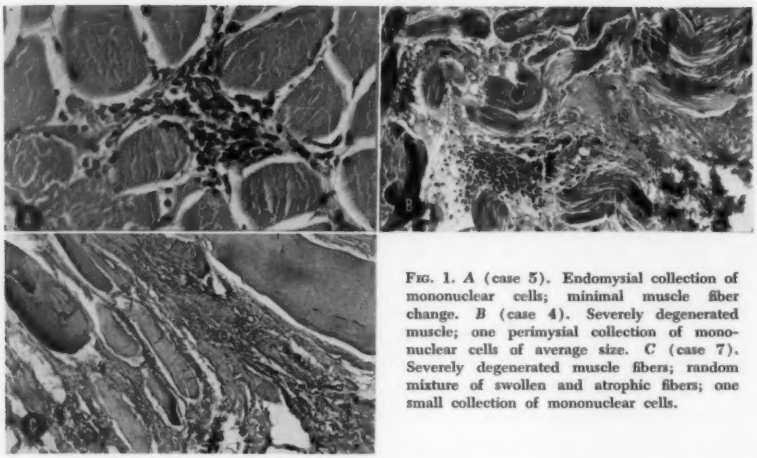

FIG. 1. *A* (case 5). Endomysial collection of mononuclear cells; minimal muscle fiber change. *B* (case 4). Severely degenerated muscle; one perimysial collection of mononuclear cells of average size. *C* (case 7). Severely degenerated muscle fibers; random mixture of swollen and atrophic fibers; one small collection of mononuclear cells.

When interstitial myositis is most prominent, mononuclear cells are diffusely disseminated throughout the endomysium and perimysium. There is a tendency, however, for collections of mononuclear cells to be found surrounding the perimysial blood vessels. Densely packed perivascular nodules of 300 to 500 or more cells may be found. Lymphocytes predominate and variable numbers of plasma cells are of common occurrence. Eosinophils may be present and, less frequently, histiocytes and macrophages can be identified.

In the average case, however, the interstitial cells are less numerous than has just been described. They are found congregated perivascularly, in accumulations numbering 20 to 100 cells. Only one or a few such nodules may be observed on each slide. If the inflammatory reaction is minor, several sections may have to be studied before nodular accumulations of lymphocytes are found.

Other abnormalities. Significant changes in other interstitial elements have not been observed. I have not found significant changes in the intramuscular nerves in sections stained with hematoxylin and eosin. I have not had the opportunity of studying sections in which an attempt has been made to stain specifically the nerves and their endings. Occasionally I have observed homogeneous, eosinophilic, acellular material in the interstitial tissue, which may represent an accumulation of mucopolysaccharides. I am not sufficiently certain that I can recognize histologic evidences of regeneration to feel justified in commenting on this point.

Investigation by others. Before closing a discussion of the findings at biopsy in polymyositis, it is necessary to review a few significant reports.

Curtis and Pollard,[9] in 1940, reported on the finding of interstitial and perivascular infiltration of lymphocytes in specimens of gastrocnemius muscle

from patients with chronic arthritis. In 1946 Steiner, Freund, Leichtentritt, and Maun[10] reported on and ably illustrated the histologic changes in muscles of patients who had rheumatoid arthritis. In some cases, at least, the abnormalities observed were indistinguishable from those I have found in cases of polymyositis, with or without the cutaneous lesions of dermatomyositis. In only one of 196 controls did the investigators named find small nodular accumulations of lymphocytes in the perimysium and endomysium, and in that case there were no associated degenerative changes in the muscle fibers.

The report of Steiner and co-authors stimulated further important studies. In 1947, with Well and Wetherby, Clawson, Nobel, and Lufkin[11] studied specimens taken for biopsy from the deltoid muscles of 44 patients who had rheumatoid arthritis. Lesions similar to those described by Steiner and associates were found in 17 cases (38.6 per cent). To determine whether or not the lesions observed were specific for rheumatoid arthritis, a study of seven muscles (pectoral, sternocleidomastoid, deltoid, diaphragm, intercostal, psoas, and supraspinatus) obtained from each of 450 routine necropsies was undertaken. Lesions corresponding to those which Steiner and associates had designated as those of "nodular polymyositis," and had believed specific for rheumatoid arthritis, were found; to be sure, these occurred most commonly in cases of rheumatoid arthritis and rheumatic fever. Frequently, however, they were encountered "in cases of death due to accident or trauma and in many cases in which death was in no way correlated with any type of acute or chronic infection."

Ogryzlo,[12] in 1948, also in an effort to determine the specificity of the lesions described by Steiner, Freund, Leichtentritt, and Maun as those of "nodular polymyositis," studied muscles obtained at biopsy or necropsy in 158 cases. He concluded that the lesions of nodular polymyositis were found most commonly in association with the so-called collagen diseases; namely, dermatomyositis, disseminated lupus erythematosus, periarteritis nodosa, rheumatoid arthritis, rheumatic fever, and generalized scleroderma. He emphasized, however, that the lesions were not specific and that he found lesions which were histologically indistinguishable from those of nodular polymyositis in cases of Addison's disease, hyperthyroidism, myasthenia gravis, "facioscapulohumeral atrophy," subacute combined degeneration, peripheral neuritis, and subacute bacterial endocarditis.

Sokoloff, Wilens, Bunim, and McEwen[13] carefully studied the frequency with which nodular collections of mononuclear cells are found in striated muscle in cases of rheumatoid arthritis. They concluded that finding of the collections was of little value in diagnosis of rheumatoid arthritis, since they were observed in 57 per cent of cases of rheumatoid arthritis and in 25 per cent of controls who had conditions other than rheumatoid arthritis, as well as in three of 13 normal controls.

Comment. From these reports and my own experience, I am forced to conclude that the pathologic diagnosis of polymyositis cannot be correlated with any one clinical entity. On the other hand, in the study of muscles

taken for biopsy from a large number of patients with miscellaneous neurologic conditions, I found interstitial myositis in only one case; in that case the condition was classic myotonic dystrophy. Bastron,[14] in a study of the frequency with which histologic abnormalities were encountered in the muscles of patients who died of diseases unrelated to clinically significant muscular or neurologic disease, found no evidence of interstitial myositis in approximately 900 slides from over 90 cases.

Steiner and others have used the term "polymyositis" to designate specific alterations in the histologic picture of muscle. This usage leads to confusion with the diagnostic term "polymyositis." It might be more accurate to use "myositis" as descriptive of the histologic picture of muscle, particularly with reference to the changes in a portion of one muscle removed for biopsy.

Electromyographic Abnormalities in Polymyositis

The electromyographic picture in polymyositis is sufficiently characteristic that in many cases Lambert[1] has been the first to suspect the true nature of the illness producing the muscular weakness. He finds the following electromyographic features characteristic of polymyositis and useful in differential diagnosis: There is increased irritability of muscle, demonstrated by the shower of changes in electrical potential resulting from insertion of the needle electrode. In studies of resting muscle, evidences of small changes in potentials are observed which are indistinguishable from the evidences of fibrillation potential found in studies of denervated muscle. During voluntary contraction there is an increase in the number of waves evidencing motor unit action potentials in comparison with the number which would be produced by a contraction of the same strength exerted by a normal muscle. The proportion of sharp spikes and polyphasic potentials of low amplitude also is increased.

Lambert's experience in electromyography in polymyositis includes a great many typical cases of dermatomyositis referred by the dermatologists and not reported in this paper.

STUDY OF CASES

The most important diagnostic features in 41 cases are presented in table 1. They are grouped as follows: Cases 1 to 19: Clinically polymyositis; histologic evidence of interstitial myositis. Cases 20 to 25: Clinically polymyositis; interstitial myositis not found. Cases 26 and 27: Clinically rheumatoid arthritis and Raynaud's disease (rheumatoid reaction type); histologic evidence of interstitial myositis present. Cases 28 to 30: Acrosclerosis with clinical evidence of polymyositis. Cases 31 to 41: Classic dermatomyositis.

Polymyositis (25 Cases)

Clinical features. The group was composed of 15 women and 10 men ranging in age from 26 to 70 years. The ages of nine patients were in the group from 40 to 49 years inclusive, the largest number of patients in any one decade of life; five were between 30 and 39 years and five between 50

TABLE 1
IMPORTANT DIAGNOSTIC FEATURES (See Study of Cases)

				Constitutional manifestations					Results laboratory determinations								
												Electromyography			Histologic changes		
Case	Sex	Age	Yrs. of symptoms on admission	Fever	Wt. loss (lbs.)	Raynaud's phenomena	Arthralgia and/or arthritis	Cutaneous manifestations	Basal metabolic rate	Sed. rate (Westergren)	Abnormalities of blood	Incr. irrit. to insertion of needles	Fibrillation potentials	Incr. proper'n. small spikes & polyphasic motor unit potentials	Interstitial myositis	Muscle-fiber degeneration	Treatment with cortisone
1	M	57	3/6	O	15	O	O	O	+16	4	None	+	+	+	+	+	+
2	M	44	3/6	O	7	O	+	O	+18	7	WBC 11,500	+	+	+	+	+	+
3	F	29	5/6	+	20	O	O	+	+15		None	+	+	+	+	+	+
4	F	43	2 1/6			+	+	+	+42	11	None	+	+	+	+	+	O
5	F	56	1 1/6	O	O	O	O	O	−7	10	None	O	+	+	+	+	+
6	M	44	5/6	O	20	O	O	O	+26	7	None		+	+	+	+	+
7	F	26	1 1/2	+		O	+	+	+39	12	None	+	+	+	+	+	+
8	M	53	5/6	+	20	+	O	O	+33	24	None	+	+	+	+	+	O
9	F	29	5/6		14	+	O	O	+12		None	+	+	+	+	+	O
10	F	44	1/6		12	O	+	O	+17		Eosin's. 12.5%	+	+	+	+	+	O
11	M	57	1/6	O	10	O	O	O	+15	54	None	+	+	+	+	+	O
12	F	36	3/6	+				+			Eosin's. 35%	O	O	+	+	O	+
13	F	44	1+	+	35	O	O	O	−7	40	None	+	+	+	+	+	+
14	M	38	11/6	O	O	O	O	O	+7	46	None	+	+	+	+	+	+
15	F	61	3	O	+	O	O	O	+23	90	None	+	+	+	+	+	O
16	F	37	1 1/2	+		O	+	+	+32	14	WBC 22,000 Eosin's. 15%	+	+	+	+	+	O
17	M	70	11/6	+	30	O	O	O		97	None		+	+	+	+	O
18	F	27	1/6+	+	6	O	O	O		53	None				+	+	+
19	F	48	3+	O		O	O	+	+8	27	Eosin's. 7.5%	+	+	+	+	+	+
20	M	33	1/6	+	40			+	O	79	WBC 12,000		+	+?	O	+	+
21	F	50	1 5/6	O		O	O	O	−6	44	None		+	+	O	+	+
22	F	41	5/6	+	10	O	O	O			None		+	+	O	+	+
23	M	48	1 1/6	+	O	O	O	O	+18	54	None	+	+	+	O	+	+
24	F	37	11/6	+		O	O	O	+36	2	None	+	+	+	O	+	O
25	M	43	11/6	+	+	O	O	+	+15		Eosin's. 16%		+	+	O	+	+
26	F	33	2+	+	10	+	+	O		53	None	O	O	=	+	+	O
27	M	34	1 1/2			+	+	O	+12	18	WBC 11,300	+	+	+	+	+	+
28	M	31	1 1/6	O	27	+		+	−5	10	None	O?	O?	+	+	+	O
29	F	60	1+	O	O	+	+	+		25	WBC 11,600	+	+	+	O	+	O
30	F	57	3	O	O	+	+	+		7	None	O	O	+	O	+	O
31	F	40	2 1/2	+	30	+	+	+			None	O?	+	+			+
32	F	51	5/6		18	+	+	+	+30		None	+	+	+	+	+	O
33	F	44	1/6	+	+	O	O	+	+37	38	L.E. clot test +	+	+	+	+	+	+
34	F	54	4					+	+2		None		+	+	O	+	O
35	F	19	3/6	+		O	O	+	−22	50	None	+	+	+	O	+	O
36	M	4	1/6	+	O	O	O	+		20	None	O	O	+	+	+	+
37	F	42	1/6	+	O	O	O	+	−6	31	None	+	+	+	+	+	O
38	F	41	3/6	+	O	O	O	+	−3	22	None		+	+	O	+	+
39	F	60	1/6	+	O	O	O	+	+16	45	None		+	+	+	+	O
40	F	35	4	O	35	O	O	+	+32	79	None		+	+	+	+	O
41	M	38	3	+	15	O	+	+	+19	66	None	+	+	+	+	+	O

O = none, or negative, except in B M R; + = present; blank = not recorded.

and 59 years; four were 20 to 29 years old; only two were more than 60 years of age.

Since dermatomyositis occurs in children, polymyositis can be anticipated also among children. In fact, the patient of case 36 was only three years of age when muscular weakness developed. This weakness I erroneously at-

TABLE 2
CLINICAL EXAMINATION OF MUSCLES (See Study of Cases for Diagnosis)

	Muscle						Distribution of Muscular Weakness				
Case	Pain	Tenderness	Induration	Atrophy	Reflexes	Contractures	Neck	Proximal muscles*	Distal muscles*	Dysphagia	Others affected
1	O	O	O	+	N	O	O	−2	−1	O	
2	O	O	O	O	N	O	O	−2	O	O	
3	O	O	O	O	−1	O	−3	−3	O	O	
4	+	+	+	+	N	+	−3	−3	O	+	
5	O	O	O	O	N	O	O	−2	O	O	
6	+	O	O	O	N	O	−2	−2	−1	+	Facial muscles
7	O	O	O	+	−3	+	−2	−3	−1	O	
8	+	+	O	O	−1	O	O	−2	−1	+	
9	O	O	O	+	N	O	O	−2	O	O	Abdomen, back
10	+	+	O	O	−1	+	O	−2	−1	+	Abdominal
11	O	O	O	+	−2	O	O	−1	O	O	Fasciculations
12	+	+	O	O	N	O	O	O	O	O	
13	+	O	+	+	−3	+	−2	−3	−2	+	
14	O	O	+	+	−3	+	O	−3	−1	O	
15	O	O	+	O	−1	O	O	−3	−1	+	
16	O	O		O	N	O	O	−2	−1	+	
17	+	+	+	+	−3	O	O	−3	−1	+	
18	+	+		+	−3	O	−3	−3	−2	+	
19	O	O	O	+	−3	O	O	−1	−3	+	Facial and palate
20	O	O	+	+	−3	+	O	−2	−1	+	
21	O	O	O	+	−1	O	O	−3	O	O	
22	O	O	O	O	−3	O	O	−3	−2	+	
23	+	O	O	+	−2	O	O	−2	O	O	
24	O	O	+	+	−3	O	−2	−3	O	O	
25	O	O	+	+	−3	O	−2	−3	−2	+	Muscles of mastication, palate, facial muscles
26	+	O	O	O	N	O	O	O	O	O	
27	+	O	O	O	N	O	O	O	O	O	
28	O	O	O	O	−3	O	O	−2	O	+	
29	O	O	O	O	N	+	O	−2	O	+	
30	O	O	O	O	N	+	O	−1	O	O	
31				+	N	O	O	−2	−1	+	Facial and sphincter muscles
32	+	+	O	O	N	O	−2	−2	−1	O	
33	+	+	+	O	−2	+	−3	−3	−2	+	Facial, tongue, palate, pharynx
34	+	+	+	+	−2	+	−2	−2	O	+	
35	O	O	O	O	−2	O	−2	−2	−1	+	Soft palate
36	+	O	O	+	−1	+	−2	−2	−1	O	
37	+	+	O	O	−2	O	−2	−2	−1	+	
38	O	O	O	O	N	O	O	−2	−1	+	
39	+	+	O	O	−3	O	O	−3	O	O	
40	O	O	O	O	−2	O	O	−3	−2	+	Ptosis, calcinosis
41	+	O	O	+	N	O	O	−3	−1	O	

N=Normal
O=Absent
+=Present
−1=Slight
−2=Moderate
−3=Severe
Blank space=not recorded

* Proximal muscles are those of the shoulder girdle, pelvic girdle, arms and thighs; distal muscles are those of the forearms, hands, legs and feet.

tributed to muscular dystrophy until cutaneous lesions and fever diagnostic of dermatomyositis appeared two and a half years after onset.

The duration of the illness in cases of polymyositis at the time of admission to the clinic tended to be short, ranging from one month to three years. Eight patients had been ill six months or less; eight for more than six and including

12 months; six for more than one and including two years; only three had been ill for more than two years.

Information is incomplete as to the duration and course of the illness subsequent to study at the clinic. One patient (case 18) died of respiratory failure five weeks after onset while under the care of one of my colleagues. I know of no other deaths in the series and one patient (case 24) is known to be living more than ten years after onset.

Fever was detected at some time during the illness in 13 of the 25 cases. In several cases fever was present only during the influenza-like illness which either precipitated or heralded the onset of polymyositis. As a rule, the temperature ranged from 99° to 101° F. In a few cases a temperature as high as 103° F. was recorded. In nine cases fever was not detected at any time in the course of the illness. In three other cases there was no record regarding this feature.

Loss of weight, ranging from six to 40 pounds (about three to 18 kg.), was recorded in 13 cases and loss of an unrecorded amount in two others. It tended to be greatest among those who experienced the greatest amount of dysphagia. However, the loss of weight often was considerable among those who experienced no difficulty in eating.

Raynaud's phenomena were present in three cases, and arthralgic symptoms suggestive of rheumatoid arthritis were present in five.

Only eight of the 25 patients had any cutaneous lesions and none of them was diagnostic of dermatomyositis. In five of the 25 patients the skin, usually that of the eyelids and face, had a violaceous coloring reminiscent of the "heliotrope" of classic dermatomyositis. When present to a significant degree, the heliotrope coloring is, to the experienced clinician, of some diagnostic importance.

Clinical examination of muscles. In table 2 pertinent observations in regard to clinical examination of the muscles are summarized. The most consistent and characteristic abnormality on physical examination was muscular weakness. Almost always the weakness was symmetrical and involved the muscles of the shoulder and pelvic girdles and of the arms and thighs.

Ten of the 25 patients with polymyositis had no detectable weakness in the muscles of the forearms, hands, legs, and feet. The neck muscles, particularly the extensors, were affected in eight of the 25 cases. In severe cases (case 18) all voluntary muscle may be weakened.

Only in case 19 were the affected muscles primarily those of the distal parts. In this case the muscles of the forehead and those about the eyes and the muscles of the legs below the knees were severely weakened. In this case the muscles of the upper extremities were strong, as were all muscles of the pelvic girdle and thighs, with the exception of the quadriceps femoris.

Atrophy of muscle was recorded in 15 of the 25 cases. In many cases in which loss of weight had been marked, it was difficult to tell whether the atrophy was a result of generalized loss of substance or of the process within

the muscle. Certainly in many cases at a stage when the muscles were very weak, atrophy was absent or was not a striking feature. In cases of longer duration the degree of atrophy often was profound.

Presence or absence of pain, contracture, and fasciculation were noted. Muscular pain was a complaint in nine cases and tenderness of affected muscles was found in only six cases. Sometimes the muscles felt flabby but in eight cases they were indurated. Contractures probably will occur in all cases of long duration unless prevented by use of stretching exercises. They were sufficient to be recorded in only six cases. Fasciculations, resembling those observed in disease of the anterior horn cells, were observed in only one case.

Muscle-stretch reflexes were normal in eight cases, and in two of these cases they were lively, approaching the upper limit of normality. Frequently the reflexes which were normal or only slightly decreased when first recorded were found to lessen in activity and to disappear while a patient was under observation.

Thirteen of the 25 patients complained of dysphagia. As a rule, it was not of much concern to the patient and its presence was elicited only in response to inquiry. However, in a case reported by Goldman[15] the bulbar symptoms were the outstanding features and the erroneous diagnosis of bulbar palsy had been made by experienced neurologists. The dysphagia most commonly was described as a sticking of solid food somewhere between the level of the manubrium and the xiphoid process. Frequently, the patient had resorted to washing the solid food down with liquids. Only one patient had regurgitated fluids through the nose.

Laboratory determinations. The basal metabolic rate was elevated (+15 per cent or higher) in 14 of the 21 cases in which it was determined. The basal metabolic rates ranged from −7 to +42 per cent. In none of the cases in which metabolic rates were elevated did consultants in metabolism conclude that hyperthyroidism was present. Not only was clinical evidence of hyperthyroidism lacking but, in many cases, determinations of protein-bound iodine in the serum and radio-iodine tracer studies supported the opinion that the patients were euthyroid.

Cells usually associated with disseminated lupus erythematosus were not found in studies of the sternal marrow or in "the L.E. clot test" in any of the five cases in which these tests were performed. However, to depart from the cases of polymyositis for a moment, in one case of classic dermatomyositis (case 33) the L.E. clot test was weakly positive.

Electromyography. In all except case 18 electromyographic studies were performed by Lambert. The electromyograms of all 24 patients tested were abnormal but in cases 5 and 12 the abnormalities were not sufficiently characteristic to be of definite diagnostic value. In case 5 electromyography was performed early in the illness, approximately one year before the diagnosis was established on the basis of clinical features and biopsy. In case 12 it was

performed three months after onset, more than two months after treatment with cortisone had been started and at a time when weakness could not be detected on tests of muscular strength. In this case, on examination of a specimen obtained for biopsy elsewhere, within the first week or two after the illness had begun, relatively normal muscle fibers and evidence of interstitial myositis were seen.

Histologic characteristics of muscle. The histologic picture was determined on specimens of muscle removed at biopsy in all cases except case 18, in which the specimens were obtained at necropsy. In all of the 25 cases except case 12 degenerative changes were observed in the muscle fibers. In cases 1 to 19 there were associated findings of interstitial myositis; in six cases (cases 20 to 25) evidence of interstitial myositis was lacking.

Dermatomyositis, Acrosclerosis, and Rheumatoid Reaction Type with Raynaud's Phenomena

Cases 26 to 41 inclusive form a group for comparison with the 25 cases of polymyositis. All patients were examined neurologically and the results recorded. Electromyograms were made in all; biopsy, in all except case 31.

Rheumatoid reaction type. In cases 26 and 27 the clinical picture resembled rheumatoid arthritis associated with Raynaud's phenomena. Although both patients complained of muscular pain, abnormalities were not detected on clinical examination of the muscles. However, on histologic study of muscle removed for biopsy, interstitial myositis and minimal focal degenerative changes in muscle fibers were found. In case 26 the electromyogram was not definitely abnormal; in case 27 it was typical of polymyositis.

Acrosclerosis. Cases 28, 29, and 30 were classified as acrosclerosis by our dermatologists. The weakness of these patients resembled in distribution that found in polymyositis. The histologic observations in case 28 were those of interstitial myositis. In all three cases degenerative changes were detected in the muscle fibers, but in cases 29 and 30 interstitial myositis was lacking. The electromyogram was typical of polymyositis in case 29; in cases 28 and 30 the only definite abnormality was a higher percentage than is normal of sharp waves and polyphasic motor unit potentials of low amplitude.

Dermatomyositis. Cases 31 to 41 inclusive seemed to resemble closely in every way the cases of polymyositis except for the presence of the cutaneous lesions diagnostic of dermatomyositis. The electromyograms were identical with those of polymyositis except in case 36, in which it was indicative of dystrophy rather than polymyositis. However, the test was performed when the patient was four years of age and the needle electrode was inserted only once. Possibly, if the examination had been as extensive as that usually performed on adults, fibrillation potentials and increased muscular irritability would have been detected.

Biopsy was performed in all cases of dermatomyositis except case 31. In seven of the ten cases so studied the combination of interstitial myositis and degenerative changes in the muscle fibers was found. In cases 34, 35,

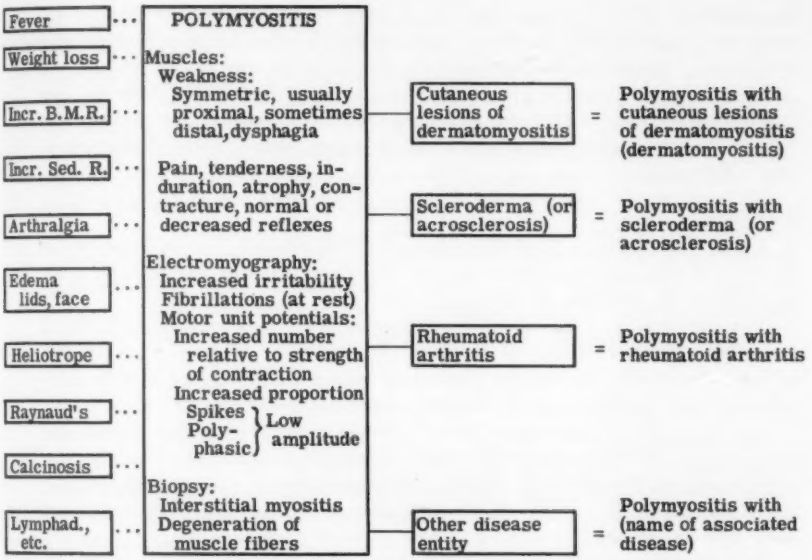

FIG. 2. An attempt to summarize graphically the perspective of neurology in regard to polymyositis. In the largest rectangle are listed the changes in muscle observed clinically, electromyographically, and histologically which characterize the entity of polymyositis. In the smaller rectangles on the left are recorded the nonspecific constitutional symptoms and laboratory abnormalities most frequently associated with polymyositis; on the right the specific clinical entities with which polymyositis may be associated. Diagnostic designations suggested to describe the combined entities more clearly are noted in the column on the right.

and 38, only the degenerative changes in the muscle fibers were observed. Since interstitial myositis is not always found in classic dermatomyositis I assume that it is not always found in polymyositis. Consequently, I believe I am justified in including cases 20 to 25 inclusive under polymyositis, although histologic evidence of interstitial myositis was lacking.

Comment

At present it seems that the muscular component in the clinical entity polymyositis and in dermatomyositis is identical. Furthermore, there is evidence for the belief that in acrosclerosis and rheumatoid arthritis the muscles occasionally become afflicted in a manner similar to that characteristic of the previous two diseases. So far I have not had the opportunity of observing, in disseminated lupus erythematosus and periarteritis nodosa, muscular changes of the type described. Should such cases be encountered, however, it will not surprise me.

Since identical clinical, electromyographic, and histologic characteristics are common to a group of related but dissimilar collagen diseases, I suggest that, in the interest of accuracy and clarity, the diagnostic use of the term

be qualified. Thus "polymyositis," used without qualification, would be appropriate diagnostically for those cases in which muscular involvement predominates. "Polymyositis," qualified by the name of the entity with which it is associated, for example, "polymyositis with rheumatoid arthritis," or "with scleroderma," would be advantageous. "Polymyositis with cutaneous lesions of dermatomyositis" could be used synonymously with "dermatomyositis" (figure 2).

DIAGNOSIS

Polymyositis seldom is diagnosed correctly at present. In only one of the 25 cases of this study had the diagnosis been made before the patients were referred to the sections of neurology.

For the most part the cases have suggested to other physicians either a neurologic disorder or one of the rare diseases. The diagnoses considered, at least tentatively, by various physicians whom the 25 patients with polymyositis had consulted are as follows: muscular dystrophy, so-called menopausal dystrophy, amyotrophic lateral sclerosis, progressive spinal muscular atrophy, myasthenia gravis, poliomyelitis, neuronitis (Guillain-Barré syndrome), psychoneurosis, thyrotoxic myopathy, Addison's disease, rheumatoid arthritis, rheumatic fever, Raynaud's disease, trichinosis, sarcoidosis, periarteritis nodosa, and brucellosis.

Polymyositis must be suspected if the complaints of any patient of any age are indicative of muscular weakness, particularly if the weakness is symmetric and predominant in the muscles of the shoulder and pelvic girdles and has become moderate or severe within a period of weeks or months. Furthermore, the weakness may be unassociated with muscular pain, tenderness, induration, atrophy, or changes in the reflexes.

The diagnosis can be established beyond reasonable doubt if, in addition to the characteristic muscular weakness, the typical electromyographic and histologic abnormalities are found. Often clinical examination and commonly utilized laboratory determinations will give supporting evidence. If the physician observes or obtains a history of fever, loss of weight, Raynaud's phenomena, pain and tenderness of joints and muscles, and edema and erythema, particularly about the eyes, his suspicions of polymyositis should be sharpened. Heliotrope coloring, particularly of the eyelids and face, is often of diagnostic value. Occasionally, leukocytosis or eosinophilia is present, but more frequent observations are significant elevations of the sedimentation and basal metabolic rates. When the basal metabolic rate is elevated, it is of particular importance to the neurologist in distinguishing polymyositis from those disorders with which he is most likely to confuse it; namely, dystrophy, atrophy, and neuronitis (Guillain-Barré syndrome). I regularly order this determination in suspected cases. Tachycardia, monocytosis, low-grade albuminuria, and high-grade creatinuria frequently are encountered but are of little help in differential diagnosis.

In concluding the remarks on diagnosis I wish to emphasize that neither

the histologic picture nor the electromyographic abnormalities described are pathognomonic of polymyositis. The diagnosis depends on finding the constellation of symptoms and on the clinical and laboratory results which characterize the entity. The more numerous the separate items of the constellation and the fewer the manifestations of other diseases, the more certain one can be of the diagnosis. For example, the histologic abnormalities which characterize polymyositis may be found in disseminated lupus erythematosus, and even in myasthenia gravis, thyrotoxicosis, and the illness resulting from infection with Coxsackie virus. In such cases the differential diagnosis will depend largely on the prominence of the role played by the manifestations of these diseases. By no means do I wish to give the impression that the diagnosis of polymyositis is easy. My colleagues and I have had difficulty in the past in being certain of the diagnosis and I anticipate similar difficulty in the future.

CORTISONE IN THE TREATMENT OF POLYMYOSITIS AND CLASSIC DERMATOMYOSITIS

I am not aware of any treatment of established value for polymyositis other than physical methods of preventing contractures. Christensen and Levison[16] have used antibiotics and have expressed the belief that good results have been obtained.

Because the course of polymyositis is variable and spontaneous arrest and improvement occur, great care must be exercised before attributing improvement to any one agent. My co-workers and I, however, have been using cortisone in treatment on the basis that polymyositis is included among the so-called collagen diseases and that patients who have these diseases are affected beneficially to varying degrees by administration of cortisone and corticotropin (ACTH). Furthermore, Shy and associates[17] have reported that treatment with cortisone has resulted in benefit in cases of "menopausal dystrophy." From study of their cases I strongly suspect that some were cases which I would classify as polymyositis. Apparently this opinion is also held by Denny-Brown.[18]

My impression as to the probable value of cortisone in the treatment of polymyositis is based on the improvement which seemed to result from its administration in five cases of polymyositis (cases 3, 6, 7, 12, and 20) and in the four of the 11 cases of classic dermatomyositis in which treatment with cortisone was given. In these cases, cortisone was administered for two months or longer and in relatively high dosage (100 mg. per day divided into four doses). Improvement in muscular strength did not become noticeable until six to eight weeks after treatment had begun although, in the cases of dermatomyositis, improvement in the dermatitis and constitutional symptoms sometimes became obvious within a week or two.

Case 6 furnishes the most striking evidence of the probable value of cortisone in polymyositis. The patient, a man 44 years of age, had been ill for approximately six months and was severely weakened at the time treatment

had begun. Cortisone, 100 mg. per day, was administered for six weeks, then 50 mg. per day for 12 weeks, and 25 mg. per day for three weeks. About six weeks after treatment had begun the man's condition started to improve and his strength had been restored almost completely ten months after the beginning of treatment.

Five other patients (cases 14, 18, 22, 23, and 25) who had polymyositis received treatment for less than two months. In case 18 death was not prevented by administration of cortisone, 1,425 mg., during the last week of life. There was no significant improvement in the other four cases of this group.

In six other cases (1, 2, 5, 13, 19, and 21) cortisone has been prescribed too recently for its effect to be known. Several of these cases will be followed with particular interest, since in them treatment was begun sufficiently early and will be persisted in for a sufficient length of time to allow definite conclusions regarding the value of cortisone in the treatment of polymyositis. In view of the extensive degenerative changes detected histologically in many of the severe cases of long duration, it is doubtful that in them cortisone can be expected to do more than arrest progression.

CONCLUSIONS AND A THOUGHT ON TERMINOLOGY

1. Polymyositis can be recognized with increasing frequency if it is realized that clinically it may be manifested by symmetric muscular weakness, without pain, tenderness, atrophy, and loss of reflexes, and without striking symptoms of systemic illness.

2. Elevation of the basal metabolic rate without other evidences of hyperthyroidism is found with sufficient frequency in polymyositis to be of diagnostic importance.

3. Electromyographic abnormalities of polymyositis are: (a) increased irritability of muscle to insertion of the needle electrode, (b) fibrillation potentials at rest, (c) an increase in the number of waves evidencing motor unit action potentials in comparison with the number which would be produced by a contraction of the same strength exerted by a normal muscle, (d) an increase in the proportion of sharp spikes and polyphasic potentials of low amplitude. These abnormalities are almost always present in polymyositis and seldom are present in conditions with which it may be confused. Hence, electromyography is one of the most important diagnostic aids in polymyositis.

4. Biopsy of muscle is an important aid in diagnosis of polymyositis.

5. There is evidence to believe that cortisone may prove to be of value in the treatment of polymyositis.

6. A change in terminology as concerns use of the word "polymyositis" would be advantageous. "Myositis" instead of "polymyositis" would be used to designate the specific alterations in the histologic appearance of muscles which have been described in the text. "Polymyositis," unqualified, would be used as diagnostic of the clinical entity in which the muscular component of the disease predominates. "Polymyositis with cutaneous manifestations of

dermatomyositis" and "dermatomyositis" would be used synonymously. If scleroderma, rheumatoid arthritis, or other entities are associated with polymyositis, the term would be qualified by the name of the associated disorder. For example, "polymyositis with scleroderma" or "scleroderma with polymyositis" would describe accurately the most significant features of the particular illness under consideration.

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It is remarkable how many distinguished literary and scientific men have suffered severely from megrim, and it would seem that some of them have succeeded in ridding themselves of the malady by the adoption of some simple hygienic measures. Such cases more particularly exhibit the benefit of bodily exercise and abstemious habits of life. "Marmontel," says Labarraque, "who was for seven years tormented by paroxysms of migraine of a very painful character, and who had consulted the Queen's physician to no purpose, cured himself by following the prescription of a farrier who advised him to drink water, to eat little, and to take exercise. Haller, too, was very subject to megrim, and he cured himself by drinking every day a large quantity of fresh water, and exchanging a highly nutritious regimen for a much lighter dietary, which had the effect of not taxing the nervous susceptibility of his stomach so much. Linnaeus again cured himself by the same means, and by taking exercise every day before dinner."

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

Clinical Evaluation of Metrazol Activation in Electroencephalography

Walter J. Friedlander, M.D.

SINCE 1949 when we first began using Metrazol as an activating agent in electroencephalography, our intent has been to use this technic as a diagnostic aid according to the method originally described by Merlis, Henricksen, and Grossman.[1] We have now done Metrazol-activated electroencephalograms in 224 patients and feel sufficiently confident to review the results and present statistics as to the clinical usefulness of this procedure.

SELECTION OF CASES

No attempt was made to subject all patients who had seizures to this procedure. Rather, individual cases were selected when it was thought that a Metrazol-activated electroencephalogram might aid in arriving at a more accurate diagnosis. The only exception to this was a series of 16 patients who were part of a special study of the effect of cortisone on the electroencephalogram[2]; none of these patients had neurologic findings or seizures. Of the total 224 patients, a definite diagnosis of convulsive disorder could be made independent of any electroencephalographic studies in 70 cases; most of these had grand mal convulsions, a few had psychomotor seizures, and none had petit mal seizures alone. Sixty-one patients, including the 16 in the cortisone study, did not have any type of episodic disorder such as epilepsy, vasodepressor syncope, narcolepsy, hysterical attacks, and so on, though they may or may not have had neurologic and/or psychiatric disease. Excluded from either group were any patients who, though they may have had generalized convulsions, had a history suggesting that their seizures were associated with alcoholism. The "no seizure" group were usually subjected to a Metrazol-activated electroencephalogram in the hope that the procedure might delineate a focus of abnormal central nervous system pathology or because, in the process of clinical work-up, a routine waking record was found to contain certain features frequently found in electroencephalograms of epileptics. All patients were adults ranging in age from 20 to 67; the average age of the "no seizure" group was 37 and that of the "seizure" group was 39.

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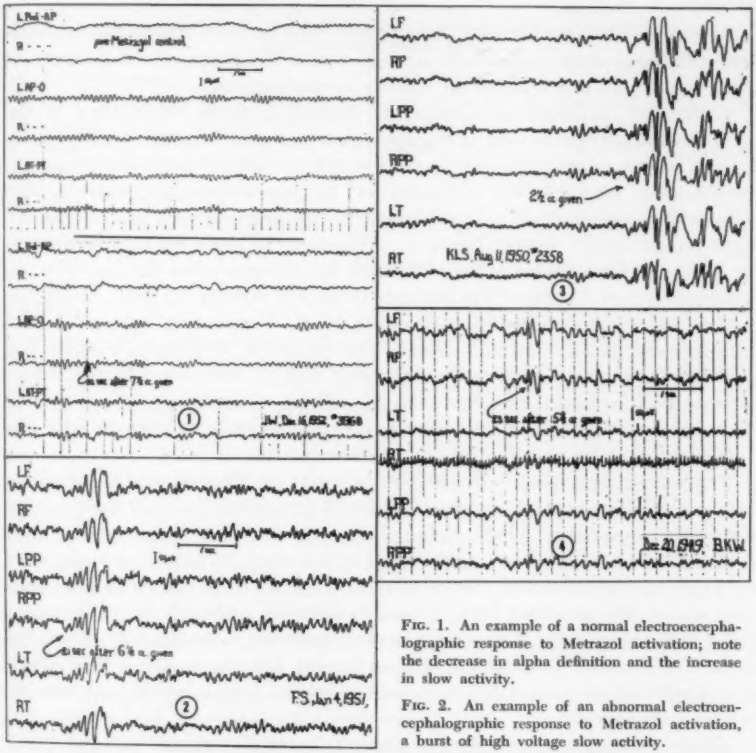

FIG. 1. An example of a normal electroencephalographic response to Metrazol activation; note the decrease in alpha definition and the increase in slow activity.

FIG. 2. An example of an abnormal electroencephalographic response to Metrazol activation, a burst of high voltage slow activity.

FIG. 3. An example of an abnormal electroencephalographic response to Metrazol activation, a burst of spike-wave complexes.

FIG. 4. An example of an abnormal electroencephalographic response to Metrazol activation, spikey waves.

TECHNIC

All patients had at least one waking electroencephalogram. The Metrazol-activated recording was obtained in the following manner: a control reading was obtained for a period of at least two minutes and then, without changing the patient's position and while continuing the record, 0.5 cc. of a 5 per cent solution of Metrazol (25 mg.) was rapidly injected intravenously every half minute until a total of 8 cc. (400 mg.) was given or until there were definite changes in the electroencephalogram. The record was continued for at least three minutes after the infusion was ended. A solution of 0.12 gm. of sodium phenobarbital in 2 or 3 cc. of water was always on hand in case the patient appeared to be on the verge of a seizure.

FINDINGS

Most patients complained of feeling tense and anxious during the infusion. These feelings were sufficiently uncomfortable to cause some patients to refuse repeat Metrazol-activated electroencephalograms.

Criteria of an abnormal response to Metrazol. Some obliteration of the normal alpha rhythm as well as the appearance of some scattered diffuse slowing was such a common finding that it was not considered abnormal (figure 1). An abnormal response was characterized by appearance of bursts of high voltage slow waves (figure 2), spike-wave complexes (figure 3), or distinct, high voltage, spikey waves (figure 4). When any of these findings were present during or for a period of three minutes immediately after the injection, or, if present before Metrazol was started, showed a definite increase during injection, the record was interpreted as abnormal. "Borderline" responses have been included in the "normal" group. The results of Metrazol administration to 224 patients are summarized in tables 1 and 2. Sixty-one per cent of 41 patients with seizures who had normal waking electroencephalograms had abnormal responses, and 14 per cent of 35 patients without seizures who also had normal waking records had abnormal responses.

Production of seizures. In the entire group of 224 patients, there was a seizure probably due to Metrazol in eight (4 per cent): five had their seizure during the procedure (which included the injection plus three minutes after the total amount was given), and three had a seizure within ten minutes after the procedure was finished. Seven of these patients were known to have seizures; the eighth is among those excluded because, although he had definite grand mal convulsions, there was a serious question as to the role of alcohol in their production. One patient was on 0.3 gm. Dilantin a day, a dose which was insufficient to control his seizures; the others were receiving no anticonvulsant medication.

Effect of anticonvulsant drugs. Sixteen "seizure" patients (20 per cent) were on medication at the time a Metrazol-activated electroencephalogram was obtained. Five of these gave false negative responses; the maximum dose of Dilantin that any of these patients was receiving was 0.5 gm. a day, although another was receiving 0.3 gm. Dilantin plus 0.1 gm. phenobarbital a day. Of the 11 "seizure" patients who had abnormal Metrazol responses while on anticonvulsant therapy, the largest daily dose of Dilantin was 0.4 gm.; one patient was receiving 0.1 gm. phenobarbital a day and one was on 4 gm. sodium bromide a day. The one case that has been listed in table 1 as "special" had an abnormal Metrazol electroencephalogram after 7.5 cc. (350 mg.) of a 5 per cent solution in March 1950, at which time the patient was receiving no medication; two and one half years later this same patient, whose seizures were now controlled with 0.4 gm. Dilantin and 0.13 gm. phenobarbital a day, had a normal Metrazol-activated electroencephalogram. It is impossible to know whether this change in response was due to: 1) the medication, 2) variation in response to Metrazol from one time to another which has been commented on by others,[3] or 3) a change in the clinical condition of the patient.

TABLE 1

DISTRIBUTION OF PATIENTS SUBJECTED TO METRAZOL-ACTIVATED ELECTROENCEPHALOGRAMS

Patients with seizures:	
Normal routine electroencephalograms, Normal* Metrazol electroencephalograms	16
Abnormal " " " " "	13
Normal " " Abnormal " "	25
Abnormal " " " " "	25
Patients without seizures:	
Normal routine electroencephalograms, Normal* Metrazol electroencephalograms	30
Abnormal " " " " "	19
Normal " " Abnormal " "	5
Abnormal " " " " "	7
Special (see text)	1
Patients who had Metrazol electroencephalograms but whose cases are not used	83
Total number of patients who received Metrazol electroencephalograms	224

*A normal Metrazol electroencephalogram is one in which, regardless of the basic pattern, there were none of the changes that have been defined in the text as abnormal alterations due to Metrazol.

Delineation of a focus. A "clinical focus" is defined as the presence of a localizing aura, a focal seizure, definite localizing neurologic findings, or pneumoencephalographic evidence of focal pathology. In 21 patients with or without seizures who had clinical evidence of a focus the following was found in the Metrazol-activated electroencephalograms: correctly localized focus in eight, a focus on the opposite side in three, and a focus in the electroencephalogram in the absence of a clinical focus in eight. In this same group, the routine waking electroencephalogram revealed a focus in the correct area in four, a focus on the opposite side in one, and a focus in the waking record in the absence of any clinical focus in three.

The average length of history of seizures in those with abnormal Metrazol-activated electroencephalogram was 2.3 years, as compared with 6.1 years in those with seizures but a normal Metrazol-activated record. When the length of history in the individual case was plotted against the minimal amount of Metrazol needed to produce a definite alteration in the record, no correlation

TABLE 2

RESULTS OF THE ROUTINE WAKING ELECTROENCEPHALOGRAM

	Total	*Normal*	*Abnormal*
With seizures	79	41 (52%)	38 (47%)
Without seizures	61	35 (57%)	26 (43%)

RESULTS OF METRAZOL-ACTIVATED ELECTROENCEPHALOGRAM

	Total	*Normal*	*Abnormal*
With seizures	79	29 (37%)	50 (63%)
Without seizures	61	49 (80%)	12 (20%)

TABLE 3

RESULTS OF METRAZOL ACTIVATION OBTAINED BY OTHER RESEARCHERS

	Method (all I.V.)	% *True Positive*	% *False Positive*	% *Seizures*	
Kaufman, Marshall, & Walker, 1947[3]	200 mg. given rapidly; max. of 500 mg.	70		27	only posttraumatic epileptics
Ziskind & Bercel, 1947[5]	100 mg./min.; max. of 250 mg.	72	18		
Cure, Rasmussen, & Jasper, 1948[6]	40 mg./min. rapidly; max. of 400 mg.	80	26	56* 3**	*epileptic patients **controls
Merlis, Henricksen, & Grossmann, 1950[1]	25 mg./½ min. rapidly; max. of 400-500 mg.	47	0		all had normal waking electroencephalograms
Cohn, Nardini, & Boswell, 1952[7]	100 mg./min.; max. of 300 mg.	41	47* 14**		*controls weighted with narcoleptics and aggressive personalities **unselected group from NP wards
Fuglsang-Frederiksen, 1952[9]	2 mg./kilo b.w. then 1 mg./kilo b.w. every ½ min. to max. of 350 mg.	82	1		
Kahn & Colony, 1953[10]	same as Cohn, 1952	75	7		all had normal waking electroencephalograms
This present series	same as Merlis except none over 400 mg.	63 61†	20 14†	4	†all had normal waking electroencephalograms

could be noted. There was no definite correlation between the age of the patient and his response to Metrazol. There was insufficient information available to see if there was any relationship between the frequency of seizures and the patient's response to Metrazol.

DISCUSSION

If there was no difficulty in making a diagnosis of a convulsive disorder in a particular patient, it was felt that Metrazol-activated electroencephalograms were not indicated; hence this series does not represent the findings in the routine waking record and the effect of Metrazol on the electroencephalogram in all our patients with seizures. This may explain the lower percentage of abnormal waking electroencephalograms in our seizure group than have been reported by others[4] and, too, may have influenced the percentage of "true positive" Metrazol-activated electroencephalograms. Hence our statistics are not necessarily applicable to all adults with a convulsive disorder but rather to that group which present some difficulties in diagnosis, for example, lack of adequate history of seizures, a history of seizures but with normal

TABLE 4
THE MINIMAL AMOUNT OF METRAZOL THAT PRODUCES ELECTROENCEPHALOGRAPHIC CHANGES

Cubic centimeters 5% Metrazol	*Per cent false positives*	*Per cent true positives*
0.5	0	3
1.0	0	6
1.5	0	9
2.0	3	10
2.5	3	11
3.0	3	15
3.5	6	18
4.0	6	19
4.5	6	27
5.0	10	29
5.5	11	37
6.0	13	38
6.5	15	48
7.0	17	56
7.5	18	58
8.0	20	65

electroencephalograms, abnormal electroencephalograms, or abnormal neurologic findings in the absence of evidence of seizures. It is felt that such a selection of patients actually offers the more realistic approach to answering the question posed by this project; that is, in the clinic is a Metrazol-activated electroencephalogram a useful aid in diagnosing convulsive disorders in adult patients?

Metrazol as an activating agent has been employed in several different ways.[1,5–12] The results of those where details of the method are given are compared in table 3. Some of the differences in results may, of course, be due to differences in technic; however, this does not explain the discrepancies in "true positives" between the series of Cohn and co-workers[7] and Kahn and Colony,[10] between the results of Jasper,[6] Merlis,[1] and this present report, or the differences in false positives between Ziskind and Bercel's group[5] and Fuglsang-Fredericksen's series.[8] Certainly an important part of these differences is due to selection of cases. Ziskind and Bercel[5] attempted to define a threshold level which would differentiate the patient with seizures and the patient without seizures. A threshold expressed in terms of probability can be accomplished with our series (table 4).

SUMMARY

1. Metrazol-activation is an unpleasant procedure for a patient and should be reserved for those in whom there is still a problem of diagnosis after the usual workup, including waking electroencephalograms, has been accomplished. However, the possibility of inducing a seizure in a person without seizures is so remote that this should not be a factor in deciding against doing a Metrazol-activated electroencephalogram.

2. Metrazol-activated records have some use in the differential diagnosis of seizures. If the response is considered in relation to the minimal amount of Metrazol needed to produce a change, a statement as to the probability of the patient having a convulsive disorder can be made. A table indicating this has been presented.

3. The "seizure" group with "false negative" Metrazol-activated electroencephalograms had a longer average history of seizures than the "true positive" group.

4. Our series is too small to arrive at any reliable conclusion about the influence of anticonvulsant medication on Metrazol-activation and the usefulness of Metrazol-activation in delineating a true focus of cerebral pathology.

5. There is still definite need for a better activating procedure.

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The naked-eye appearance of the nerve-centres in idiopathic epilepsy is for the most part that of healthy organs. The slight opacity and thickening of the meninges in some cases of long duration, and the more distinct signs of meningitis sometimes seen after death in the status epilepticus, are apparently merely secondary changes. If the patient has died in a fit, the post-mortem appearances are those of the intense venous engorgement which is so conspicuous during life, and they differ little from those met with after ordinary asphyxia.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Carpal Tunnel Syndrome in Acromegaly

Francis Schiller, M.D. and Felix O. Kolb, M.D.

THE clinical features of partial thenar atrophy[1] in both its unilateral and bilateral form were originally described by Hunt.[2] Marie and Foix,[3] reporting the autopsy of such a case, called attention to the compression of the median nerve by the thickened transverse carpal ligament. List[4] was the first to describe bilateral median neuropathy as a complication of Marie's disease, or acromegaly. The only other cases of acromegalic median neuropathy reported are Woltman's[5] two patients found among 213 cases of acromegaly, and three cases recently published by Kellgren and co-workers.[6] The frequent complaint of digital numbness and paresthesias in acromegaly suggests, however, that the syndrome may be more common in this disease than has been realized. The presence of a thickened transverse carpal ligament would not be surprising considering the general tissue overgrowth so typical of acromegaly.

Marie and Foix[3] and Moersch[7] advocated surgical decompression of the median nerve for the relief of digital pain, from which patients with partial thenar atrophy frequently suffer. Since 1941 this operation has been successfully performed in many nonacromegalic cases[8–13] and in one acromegalic patient.[6] The terms "carpal tunnel syndrome," "partial thenar atrophy," "median neuropathy" or "neuritis," and "tardy median palsy," have thus become synonymous.

In their acromegalic cases both List[4] and Woltman[5] observed improvement in the median neuropathy following roentgen therapy of the eosinophilic pituitary adenoma. As this treatment often succeeds in decreasing the soft tissue volume of acromegalic hands in general,[14] it may be expected to reduce the pressure in the carpal tunnel as well and thereby relieve the pain of the compressed median nerve.

This report describes an acromegalic patient who showed the full syndrome of bilateral median neuropathy, with sensory improvement following surgical removal of the pituitary tumor. Three other examples of this syndrome are also described briefly, in two patients with acromegaly and one with myxedema. The muscle changes are demonstrated by means of simple handprints.

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Finally, some of the current theories regarding the carpal tunnel syndrome are reviewed with reference to patients with endocrine disorders.

CASE REPORTS

Case 1.—Advanced acromegaly with bilateral partial thenar atrophy; paresthesias followed by pain and eventual anesthesia in median nerve distribution; some recovery of sensation after surgical removal of eosinophilic pituitary adenoma.

A 38 year old white truck driver was admitted to the University of California Hospital in November 1950. He complained of headaches during the previous three years and failing eyesight over the past three months. Ten years prior to admission he first noticed progressive enlargement of his face, hands, and feet; loss of libido and general fatigue had been noticeable for five years.

Two years after his hands began to enlarge (eight years before hospital admission) he was disturbed by tingling and pain occurring simultaneously in the thumb, index, and middle fingers of both hands. The pain was excruciating at times, especially at night when he found that suspending his hands over the bar of his bed would give him some relief. The tingling extended at first along the radial side of the forearm as far as the elbow, but this symptom disappeared after a few weeks. Over a period of many months the pain and tingling of his hands grew less, but at the same time the ability to feel the texture, shape, and temperature of objects was gradually lost in the affected fingers. For some months or years he had been unable to use those fingers in discriminating and handling objects.

Examination showed a large man with coarse and rather immobile features, a fleshy nose, thick lips, a massive tongue, and huge chin. Hands and feet were of enormous size. The skin was generally thickened and hyperhydrotic. Visual acuity was 20/50 in the right eye and 20/30 in the left eye; the fundi were normal; a bitemporal upper quadrant anopia was present. He was mentally alert and of average intelligence but seemed emotionally flat, somewhat withdrawn, and slowed down in his reactions.

Roentgenograms showed thickening of the calvarium, marked enlargement of the pituitary fossa, and thinning of the posterior clinoid processes. The jaw and air sinuses were enlarged. The cervical and thoracic vertebrae were enlarged and showed some evidence of hypertrophic arthritis. Hands and feet showed no change in the bony architecture except for tufting of the terminal phalanges and areas of cystic rarefaction in the left triquetrum and capitate bones. The carpal canals were not encroached upon by bony anomalies.

Neurologic abnormalities, except for the visual field defect mentioned, were confined to the massive hands. Figure 1 shows the almost horizontal groove at the base of each thenar eminence, resulting from the wasting of abductor pollicis brevis. Abduction of the thumbs in a plane at right angles to the palm was practically absent, and maximal lateral abduction of the thumb was reduced to an angle of about 60 degrees between thumb and index finger (normal 90 degrees and over).[15] There was no wasting or weakness in other muscles of the hands, yet he was unable to close his fists owing to the thickened soft tissues of the fingers and palms. Figures 1 and 2 show the area of complete anesthesia to touch, deep pressure, cold, and pinprick involving parts of the thenar, thumb, index, and middle fingers of both hands in a typical median nerve distribution. Vibration sense was lost over the tips of the thumb, index, and middle fingers of both hands, but was preserved over the heads of the metacarpals and phalanges. Position sense was lost in all phalangeal joints of the index and middle fingers of both hands and impaired in both thumbs. Deep pressure of either median nerve at the wrist, but not elsewhere, was painful locally. Percussion at this point (Tinel's sign)[16] produced tingling confined to the thumb, index, and ring-finger, areas affected by anesthesia. Warming of the body failed to raise the temperature of the affected nail beds (index and middle finger) by more than

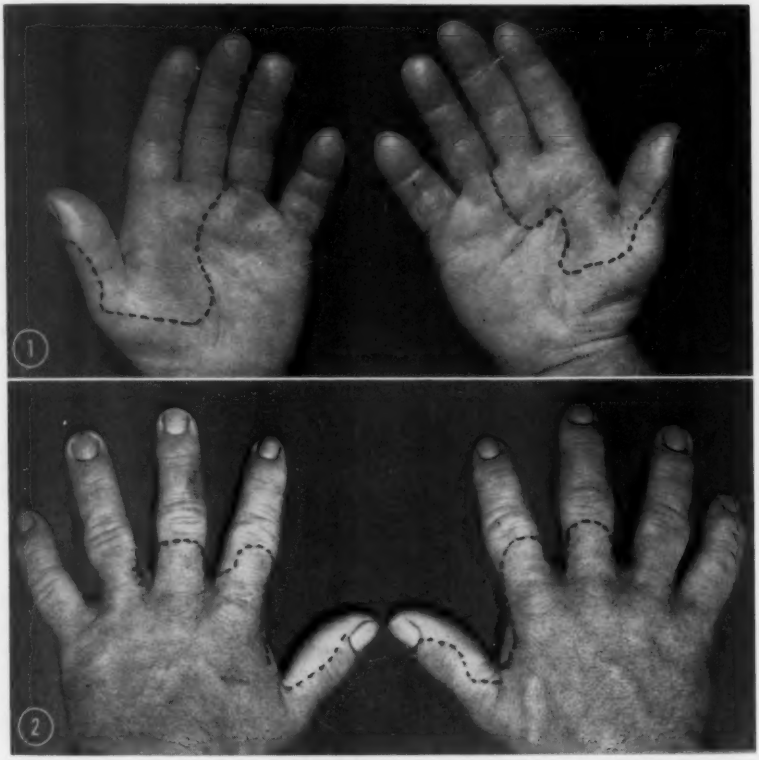

FIG. 1. *Case 1.* Acromegalic hands with horizontal groove at proximal margin of each thenar eminence corresponding to wasted abductor pollicis brevis. Area of anesthesia in median nerve distribution distal to dotted line.

FIG. 2. Dorsum of same hands shown in figure 1. Area of anesthesia affecting fingers in median distribution distal to dotted line.

2 degrees Centigrade, while the unaffected nail beds (thumb, little finger, and great toe) showed increases in temperature of 10 degrees Centigrade. Electromyography of the thenar failed to show any denervation action potentials, possibly owing to complete fibrosis of the single small affected muscle.

On December 4, 1950 a sizable eosinophilic pituitary adenoma was removed. The patient went through a stormy postoperative period due to left ventricular failure, and had a transient left facial palsy.

Daily examinations of the sensation of his fingers revealed, on the eighth postoperative day, a slight improvement of sensation in the affected area of both hands where pinprick and rubbing could just be perceived. Position sense in the phalangeal joints also returned, and the patient was able to recognize objects by palpation at the time of his discharge from the hospital on the twentieth postoperative day.

One month later his visual fields and visual acuity had returned to normal. He reported that a certain pair of gloves, which had been too small before operation, now fitted

nicely. There was no objective improvement in the motor and sensory findings pertaining to the median neuritis beyond that noted at the time of discharge from the hospital.

Similar findings were obtained on May 1, 1951 and July 2, 1952 after one poorly tolerated course of x-ray therapy. Electrical stimulation of the ulnar nerve gave a normal response and no contraction of the superficial thenar muscles. Stimulation of the median nerve above the wrist resulted in a slight contraction of opponens pollicis, indicating a minimum of conduction in the median nerve. When last examined in May 1953 the patient's general condition had remained fair under supportive treatment with androgens.

Case 2.—Acromegaly with bilateral partial thenar atrophy; slight paresthesias, but no sensory loss; apparently stationary.

A 41 year old Armenian housewife entered the Massachusetts General Hospital in November 1950, with a seven year history of progressive increase in the size of her hands and feet following her last pregnancy. Within a short period her ring had to be enlarged from size 8 to size 12. She complained of right temporal headaches but no visual disturbance. Her menses remained regular after parturition, but lactation continued for about two years. Except for occasional paresthesias of the hands and feet, there were no complaints referable to the limbs.

Examination revealed the classical features of acromegaly. The visual fields were normal. A drop of colostrum-like substance of pH 7.5 was readily expressed from each nipple. The hands and feet were huge and fleshy, the fingers "spade-like," and excessive skin folds covered both palms and wrists; the lines of the palms were widely spaced in a "simian" pattern. In addition, there was a striking bilateral partial atrophy of the thenar eminence without any gross sensory loss (figures 3 and 4).

X-ray examination showed huge frontal sinuses and enlargement of the sella turcica. The hands showed marked tufting of the terminal phalanges and soft tissue swelling. There was no gross bony abnormality in the region of the carpal tunnel.

The volume of both hands and feet was 3900 cc.[14] The fasting blood sugar was 100 mg. per cent with slight insulin insensitivity, but with hypoglycemia responsiveness. All the electrolytes were within the normal range except for a moderately elevated serum phosphorus of 4.7 and 4.2 mg. per cent. The F.S.H. (pituitary gonadotrophin titer) was positive for 6.5, 13, and 52 mouse units.

The patient was treated by a course of x-ray to the pituitary (total 3200 r), resulting in slight improvement of headaches. When last seen six months later there was no subjective or objective change in the appearance of the hands. A course of estrogen therapy was contemplated.

Case 3.—Asymptomatic bilateral partial thenar atrophy discovered 35 years after onset of acromegaly; no sensory loss. (Reported in part elsewhere.[17])

A 56 year old white male insurance agent was first seen in May 1936 with the complaint of numbness and paresthesias of the extremities ascribed to "Raynaud's disease" for some 20 years. He had been married for 26 years and had three children. Ten years before a friend first called attention to his acromegalic features. The patient thought these had become more marked since then, but denied any increase in the size of his face, hands, or feet. Two years before examination he first noticed separation of the teeth, a dorsal kyphosis, and forward bulging of the chest. Other complaints were weakness, loss of energy, easy fatigability, a voracious appetite, increased sweating, and slight progressive blurring of vision.

Examination showed a tall and well-developed, but somewhat undernourished patient. He had a marked dorsal kyphosis and a barrel-shaped chest. His skin was thick, warm, and moist, the superciliary ridges moderately enlarged, and the nose broad. There was moderate prognathism, separation of the teeth, and enlargement of the tongue. Examination revealed haziness of the lens, marked myopia, and upper bitemporal quadrantanopia.

FIG. 3. *Case 2.* Patient's acromegalic hand (left) with normal hand (right) for comparison. Note patient's spade fingers, loss of normal contour of palm, excessive skin folds, and thenar atrophy.
FIG. 4. Hand and foot print of acromegaly in case 2 compared with normal. Note fine details of structural changes, for example, defect in thenar eminence of acromegalic hand, in addition to other typical "simian" features, such as loss of contour, coarsening and widening of sulci, and so on. Similar changes are seen in the foot.

The hands and feet were slightly enlarged, and the fingers and toes broader than normal. The rest of the neurologic examination was normal.

Routine laboratory examinations were normal, including fasting blood sugar and glucose tolerance tests. The basal metabolic rate varied between plus 8 and plus 26. Roentgenograms showed a thickened skull, enlargement of the sella turcica, air sinuses, and mandible, with separation of the teeth and tufting of the terminal phalanges of the hands and feet.

The patient received 10 minims of Lugol's solution daily and two courses of deep x-ray therapy, 960 r, to each of the temporal and frontal regions without apparent change in his condition.

He was not seen again for some 15 years, when he was re-admitted to the Massachusetts Eye and Ear Infirmary in 1951 because of difficulty in breathing and hoarseness. Reexamination revealed a substernal goiter in addition to the signs of advanced acromegaly. The hoarseness was caused by a vocal cord palsy, presumably due to pressure on the recurrent laryngeal nerve. Examination of the hands now showed marked bilateral partial thenar atrophy, with complete wasting of the radial portion of the thenar eminences. In view of the lack of complaints referable to the hands and his poor general condition, no further studies in this direction were undertaken.

Case 4.—Advanced myxedema; intercurrent unilateral sensorimotor median neuropathy during treatment.

A 59 year old white housewife and mother of three children was first seen at the University of California Endocrine Clinic in May 1951, complaining of obesity, progressive cold intolerance, fatigability, hoarseness, and dyspnea. Thirteen years earlier her weight had been 330 lbs. and during this period she had taken from 6 to 8 grains of thyroid daily with insufficient benefit. The previous history noted an attack of nephritis in childhood and bilateral wrist fracture in 1938.

On examination she weighed 290 lbs., had a croaking voice, dry and scaly skin, and periorbital edema. The basal metabolic rate was minus 14, and serum cholesterol was 320 mg. per cent. An electrocardiogram on October 31, 1951 showed a complete right bundle branch block which had disappeared by December 5, 1951. At this time the metabolic rate was minus 29, serum cholesterol 736 mg. per cent, nonprotein nitrogen 66 mg. per cent, protein bound iodine 3 micrograms, and radioactive iodine uptake reduced. The urinary 17-ketosteroids excretion was 1.5 mg. in 24 hours; urinary F.S.H.: positive at 5 mouse units, negative at 80 (low for menopause).

On an 800 calorie diet, mercurials, and later thyroid medication, her metabolic rate returned to plus 4 in June 1952. On October 2, 1952, her general condition was much improved and her weight reduced to 194 lbs., with serum cholesterol down to 299 mg. per cent and protein bound iodine 5.4 mg. per cent. At this time she called attention to annoying tingling sensations in the thumb and index finger of her right hand which had been present for the past year. This symptom had started six months after initiation of treatment.

Examination revealed slight wasting and marked weakness of abductor pollicis brevis and moderate weakness of flexor pollicis brevis on the right side. Paresthesias and hyperalgesia were present in the right thumb and index finger. Roentgenograms of both wrists showed no disease of bones or signs of old fracture.

The patient was last seen in September 1953; there was no detectable thenar atrophy, but slight sensory impairment.

DISCUSSION

Sensory Manifestations

As Woltman[5] has pointed out, there is no reason to assume that partial thenar atrophy in acromegalic cases is essentially different from that occur-

ring spontaneously. Despite the fact that extensive reviews of acromegaly, such as those by Sternberg,[18] Atkinson,[19] and List,[4] reveal no clearcut cases of this syndrome, the digital paresthesias which are so common in these patients may be more often confined to the median nerve territory than has hitherto been realized. The incidence of paresthesias was found to be 30 in 100 acromegalic patients examined by Davidoff.[20]

In his classic monograph on acromegaly Sternberg[18] speaks of "pains of various kinds, and in all possible parts of the body," of acroparesthesias "often associated with a feeling of numbness appearing chiefly at night . . . It belongs to the earliest appearances of the disease . . . and is possibly the result of changes in the cutaneous nerves, but possibly also of the early cessation of the menses . . . The pain and paresthesia . . . rarely endure when acromegaly is fully developed. But in some cases very violent pains continue permanently. . . . Lightning pains as in tabes also occur. Pronounced disturbances of sensibility . . . are rare. True paralyses do not occur except in the cranial nerves. Here and there muscular atrophy is found in the region of individual nerve trunks affected with neuritis."

The first acromegalic patient reported with this syndrome[4] showed pain and tingling of the thumb, ring, and index fingers of both hands, followed by anesthesia. These pains and paresthesias preceded the visible enlargement of the hands and receded after roentgen therapy to the pituitary fossa; however, there was no definite thenar atrophy at any time. One of Woltman's[5a] two patients had pain in the hands for five years and numbness for one, with bilateral weakness and atrophy of the thenar muscles, again with improvement following roentgen therapy to the sella. Our own cases showed all degrees of discomfort, from severe pain and paresthesias in case 1 to practically no complaints in cases 2 and 3. Tingling may be followed by pain and both disappear with complete cessation of nerve conduction (anesthesia).

While paresthesias are a common complaint, objective sensory impairment is reported in about one-half of the nonacromegalic cases. Yet the recent careful study by Kremer and co-workers[13] reveals the typical sensory loss in 35 out of 40 cases with acroparesthesias. The extent of sensory impairment in the distribution of the median nerve is best demonstrated in our case 1. Brain and co-workers[8] maintain that the sensory abnormalities associated with muscle wasting are most important in the differential diagnosis of the carpal tunnel syndrome: the distribution of sensory impairment differentiates this syndrome of nerve compression at the wrist (involving C6-C7) from other neurologic disorders affecting the hand, such as the costoclavicular syndrome (involving C8-T1).

One sign of prognostic importance is percussion of the nerve trunk which may give rise to tingling in the periphery of the nerve (Tinel's sign).[16] Recovery of function was seen both in our first patient and in those reported by Phalen,[11] who showed a positive response to this test. Another sign indicative of compression of the median nerve is elicited by sudden flexion of the wrist, which may give rise to pain in the area supplied by the nerve.[11]

With surgical decompression at the wrist, recovery of sensation may occur in all types; in the acromegalic variety roentgen therapy or removal of the pituitary tumor, as in case 1, may as well be effective in restoring sensation and abolishing dysesthesia.

Motor Manifestations

Objective signs of motor loss were more common than those of sensory impairment, in both the present cases and those in the literature. Brain and co-workers[8] have explained this preponderance on the grounds that compression of a nerve damages motor fibers first. Not all the thenar muscles are equally affected; typically, abductor pollicis brevis and sometimes opponens pollicis are weak and wasted, while flexor pollicis brevis escapes. In our cases abductor brevis seemed to be the only muscle involved. The difference in degree of involvement of some muscles supplied by the median nerve, or even the complete absence of motor involvement (List's case), might be explained by Highet's[21] observation that the ulnar nerve may supply part or all of these thenar muscles. This explanation, however, did not seem to hold when the respective nerves were stimulated in case 1. Another reason for the partial thenar involvement, given by Saunders,[22] is the possibility of injury to individual branches of the median nerve, supplying opponens pollicis and abductor brevis separately, the latter most superficial branch being more prone to occupational trauma. This may also explain the not infrequently observed presence of unilateral thenar atrophy, if indeed repeated trauma is an important factor.

While some return of muscle power can be anticipated with prompt treatment, irreparable damage is likely to occur in long-standing cases. By and large, return of sensory function is more likely than motor.

Etiology and Therapy

A number of observations have been published linking acromegaly to various central nervous system diseases characterized by muscle wasting and sensory disturbance. Clinical pictures indistinguishable from motor neuron disease and even syringomyelia have been described and reviewed.[4,18,19,23,24,25] The manifestations of partial thenar atrophy, however, are sufficiently well established to allow the exclusion of the present patients from the diagnosis of spinal or cerebral pathology.

There can be little doubt that in the present cases there are peripheral nerve lesions affecting the motor and sensory territory of the median nerve. Evidence of severe cervical spondylarthritis and other features of cervical radiculitis, made responsible for partial thenar atrophy by Gronemeyer,[26] were lacking in these cases and those of the recent literature.

It is necessary to find a common denominator for the spontaneously-occurring carpal tunnel syndrome and that seen in cases of acromegaly, or, rarely, myxedema. The basic anatomic disturbance must be compression of the median nerve at the wrist. Here the nerve and flexor tendons pass into the palm

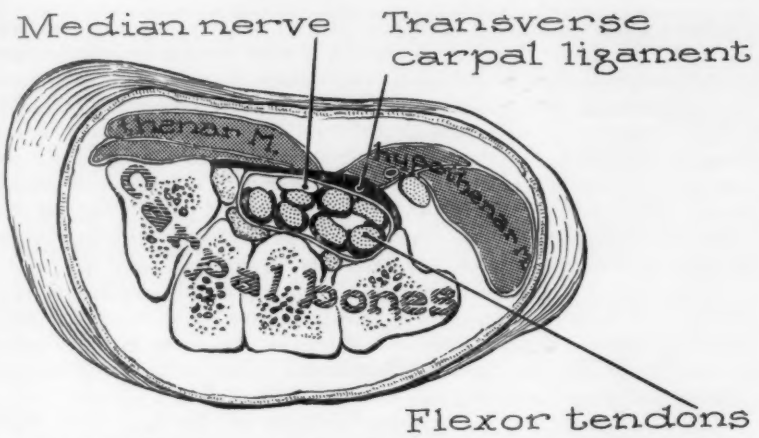

FIG. 5. Schematic cross section of carpal tunnel. Note position of median nerve between transverse carpal ligament and flexor tendons.

through the rather tight carpal tunnel formed by the rigid transverse carpal ligament above and the carpal bones below (figure 5). In acromegaly the principal disturbance is the overgrowth of soft tissues and skin, far in excess of the limits set by comparatively lesser changes in the unyielding skeleton. In gigantism, when the epiphyses are still open, the bony framework keeps pace with the enlarging soft tissues, and consequently the typical coarsening of features, excessive skin folds, and so on, of the acromegalic do not occur. This is graphically demonstrated by the handprints of a giant compared with those of an advanced acromegalic (figure 6). Encroachment on nerve structures in the carpal tunnel of acromegalics may thus be expected. A similar mechanism, that is, nerve compression by soft tissue overgrowth, might possibly have caused the vocal cord palsy observed in case 3, as described previously by Grotting and co-workers.[27] In the present cases and in those reported by List,[4] Woltman,[5] and Kellgren and co-workers,[6] this encroachment was not due to bony overgrowth but rather to the increased bulk of soft tissue. The rapid improvement after successful irradiation of the pituitary, noted by List,[4] Woltman,[5] and in case 1, also makes bony enlargement an unlikely factor in nerve compression. Moreover, the striking and rapid decrease in the volume of hands and feet by either surgical, roentgen, or estrogen therapy, which Albright and co-workers[14] noted in some successfully treated acromegalics (figure 7), is in favor of a decrease in soft tissue rather than bony framework. It is likely that a similar encroachment of the median nerve by myxedematous tissue occurred in case 4.

Hunt,[2] as well as most of the later authors who share the mechanical point of view, believe that repeated occupational trauma is mainly responsible for the thickening of the transverse carpal ligament. But, as Wartenberg[1] has

pointed out, the syndrome is commonly bilateral and seen in housewives past the menopause rather than in men exposed to wrist trauma, such as dentists, cabinet makers, locksmiths, and so on. These observations would make trauma an aggravating or precipitating, but hardly a primary etiologic agent. The surgical evidence for a mechanical pathogenesis, on the other hand, is too strong to uphold the hypothesis of an "abiotrophy of such phylogenitally recent structures as the small movers of the thumb."[1] Ischemia and venous stasis as additional factors have also been considered.[6] A possible familial predisposition is suggested by the observation of partial thenar atrophy in three sisters[28] but these patients, too, had passed the menopause.

While it is most likely that the median nerve is primarily compressed from without by a thickened ligament, the crowding in the carpal tunnel may possibly be occasioned by an intrinsically enlarged median nerve, that is, a nerve thickened by the increase of its own endoneural connective tissue.[4] This condition, found above the constriction and often referred to as a "neuroma," may be due merely to pressure and edema. But Marie and Marinesco[29] also have described generalized endoneural overgrowth in the peripheral nerves of acromegalics.

Regardless of these considerations, it seems significant that this syndrome occurs principally in patients with certain endocrine disorders, that is, in females past the menopause and cases of acromegaly. Advanced osteoarthritic changes of the spine, commonly seen in both conditions, do not seem to be a likely factor.[3,6,8,26] As has been pointed out by Albright and co-workers,[14] "acromegaly resembles the postmenopausal state in that both show (1) a high serum inorganic phosphorus level, (2) negative calcium and phosphorus balances, and a tendency to osteoporosis, (3) a drop in serum phosphorus level and retention of calcium and phosphorus with estrogen therapy." A certain coarsening of features is seen in the menopause as well.

Assuming that estrogens suppress the pituitary, does the hypogonadal state of the menopause conversely bring out the proliferative effects of pituitary growth hormone? The effects of such stimulation on connective tissue growth would be most likely to appear in a tight compartment such as the carpal tunnel. In that case treatment with estrogens in the early stages of the disease seems logical. Three cases of menopausal median neuropathy have been observed by the authors where this treatment has, in fact, caused digital pain to disappear.

Thus, early diagnosis of wrist compression of the median nerve in postmenopausal patients complaining of pains or paresthesias in the hands might lead to successful treatment with estrogens before section of the transverse carpal ligament becomes necessary. In cases with acromegaly or, more rarely, myxedema, one might equally aim at the reduction of soft tissue in the carpal tunnel by appropriate therapy of the endocrine disorder. In so doing one can hope to forestall pain and permanent damage to the sensorimotor functions of the hands.

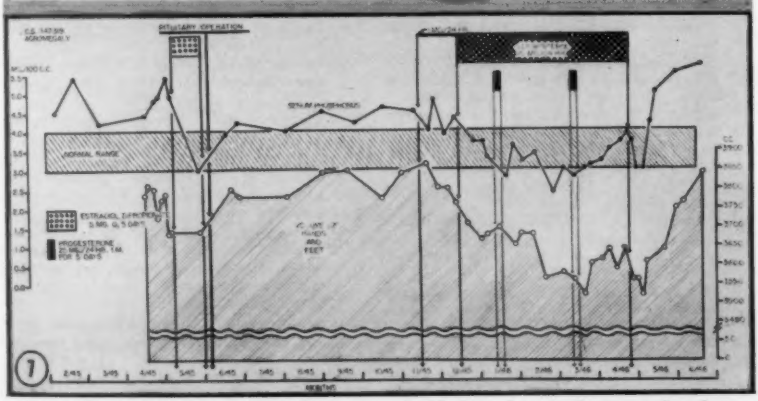

FIG. 6. Hand prints of acromegalic subject compared with those of a normal person and a giant. The huge hand of the giant shows none of the features of the acromegalic, since the bony skeleton has kept pace with the excessive soft-tissue growth.

FIG. 7. Change in volume of hand and feet after pituitary surgery and during estrogen therapy of an acromegalic. Note the parallel changes in serum inorganic phosphorus (From Albright, Reifenstein, Forbes, and Bartter).[34]

SUMMARY

1. The carpal tunnel syndrome (partial thenar atrophy) is described in three patients with acromegaly and in one with myxedema.

2. These cases are compared with the more common syndrome of spontaneous partial thenar atrophy. Its principal occurrence in women past the menopause suggests an endocrine rather than a primarily traumatic etiology for most cases with this syndrome.

3. A trial with estrogen therapy is advocated in the early stages.

The handprint method of demonstrating muscle changes was suggested by Dr. Lawrence Arnstein. We are indebted to Drs. E. B. Boldrey, Ellen Brown, and R. F. Escamilla of the University of California School of Medicine, for permission to use their records in cases 1 and 4, and to Drs. F. Albright, W. Bauer, and J. Stoeckle of the Massachusetts General Hospital for their records in cases 2 and 3.

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Metabolic Reactions to Cold Stress of Rats with Hypothalamic Lesions

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THE CONCEPT that an intact hypothalamus is necessary for normal metabolism is not new. In 1885 Aaronson and Sachs,[1] by puncturing the tuber cinereum of cats, increased the carbon dioxide output and also produced consistently high body temperatures. Later Andreu-Urra,[2] by injecting silver nitrate into, and Mazzaco,[2] by placing lesions in the tuberal areas of the hypothalami of dogs, found metabolism to be reduced below basal levels.

Although the results of these early investigations are contradictory in some respects they do establish a relationship between the hypothalamus and changes in metabolism. More recent evidence demonstrating precise anatomic locations of functional centers within the hypothalamus[2] minimizes the significance of these early contradictions, and indeed such contradictions lend strong support to the regulatory nature of the hypothalamus, that is, its ability to either inhibit or stimulate vegetative functions in meeting body requirements.

The homeothermic animal is able to maintain an optimum body temperature when exposed to cold by both increasing and conserving body heat. The increase in body heat is made possible by an increase in metabolic rate (as measured by oxygen utilization) and a conservation of body heat by general peripheral vasoconstriction. Benedict and MacLeod,[3] Adolph,[4] Sellers, You, and Thomas,[5] and Buchanan, Witt, Roberts, and Massopust[6] all have demonstrated increased metabolic rate during cold stress. Sellers, You, and Thomas, experimenting with clipped rats, believe this to be the principal means of increasing the body temperature while the effects of vasoconstriction are negligible. On the contrary, Bazett[7,8] affirms that peripheral vasoconstriction enhanced by cool blood passing through the hypothalamus is the primary reaction in maintaining homeothermia during cold stress. He is in part supported by the experiments of Barbour, McKay, and Griffith[9] who have shown that reflexive

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vascular changes upon exposure to cold are initiated in the anterior hypothalamus. Adolph[4] has demonstrated that metabolic mechanisms eventually fail during prolonged cold stress and Barbour, McKay, and Griffith[9] that vasoconstrictor mechanisms also fail. The mechanisms influencing body metabolism seem to be located in the tuberal area of the hypothalamus and mechanisms associated with vascular reactions seem to be located in the anterior hypothalamus.[1,2,3,5,7,8,9] The present investigation, which involved careful measurements of oxygen consumption rates and body temperatures of rats with lesions in the hypothalamus, has been carried out with the objective of determining whether there are functional areas in the hypothalamus which correspond with those described in the investigations referred to above.

MATERIALS AND METHODS

Sprague-Dawley rats in the weight range of 120 to 150 gm. were used throughout this experiment. The rats, anesthetized with ether, were mounted in a stereotaxic instrument recently described by Sherwood, Massopust, McCrum, and Buchanan,[10] and electrolytic lesions were placed in various areas of the hypothalamus.

The apparatus used for measurement of oxygen consumption consisted of spirometers and kymograph which recorded rates of consumption, and a Brown potentiometer for synchronous and continuous recordings of the environmental temperatures. Body temperatures as measured in the high colonic regions of the rats were also recorded by the Brown potentiometer. Certain modifications have been incorporated in the apparatus as originally described by Buchanan, Witt, Roberts, and Massopust.[6] Low-pressure gas valves were inserted into the oxygen delivery system between the bell-type spirometer which served as an oxygen reservoir and the recording spirometers. By means of a "Y" tube inserted between the gas valves and the recording spirometers, oxygen was conducted through a rubber tube to supply the chambers in which the rats were placed. The recording arm inscribed the rate of emptying of the spirometer on electrosensitive kymograph paper. Two pairs of electrical contacts were built into the spirometer stand and were triggered by the recording arm. These electrical contacts opened and closed the gas valves on emptying and filling of the spirometer.

A deep freeze, with a thermoregulator attached to the freezing system, kept the contained water bath at a constant temperature of 10° C. The rats, placed in cages within the metabolism chambers, could shiver and respire without restriction but were somewhat limited as to other movements. Chambers were immersed for approximately one-half hour before recordings of oxygen consumption and temperature were made. This allowed for contraction of the gas and proportionate replacement at the reduced temperature of the chamber. Carbon dioxide and excess moisture in the chambers were absorbed by soda lime and Drierite. Temperature and oxygen consumption rates were recorded for two and one-half hours for each experiment. Differences in oxygen consumption rates rather than actual values were of primary in-

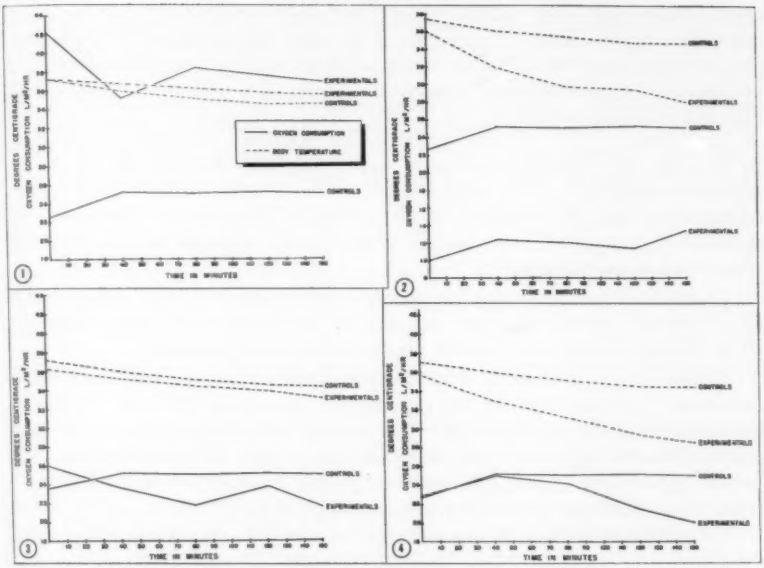

FIG. 1. Graph showing the average oxygen consumption rates and body temperatures of rats in the first experimental group (lesions in posterior hypothalamus).

FIG. 2. Graph showing the average oxygen consumption rates and body temperatures of rats in the second experimental group (lesions in dorsal tuberal hypothalamus).

FIG. 3. Graph showing oxygen consumption rates and body temperatures of rats in the third experimental group (lesions in ventral tuberal hypothalamus).

FIG. 4. Graph showing oxygen consumption rates and body temperatures of rats in the fourth experimental group (lesions in anterior hypothalamus).

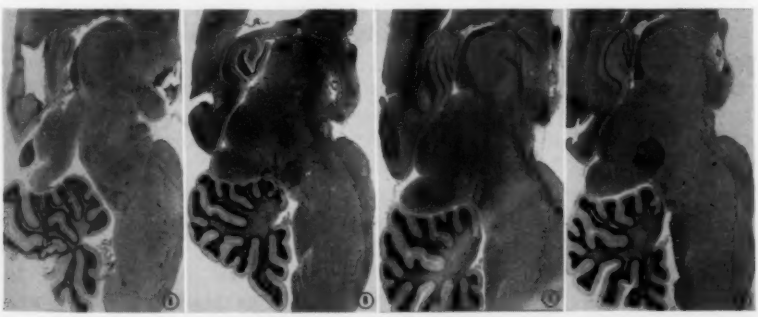

FIG. 5. Photomicrograph of typical posterior hypothalamic lesion.

FIG. 6. Photomicrograph of typical dorsal tuberal hypothalamic lesion.

FIG. 7. Photomicrograph of typical ventral tuberal hypothalamic lesion.

FIG. 8. Photomicrograph of typical anterior hypothalamic lesion.

terest. Each spirometer volume of gas used was corrected 3.7 ml. for every one-tenth degree centigrade change in chamber temperature. Oxygen consumption volumes obtained were converted to six-minute intervals and reduced to standard temperature and pressure by means of a nomograph constructed from the basic formula: $\left(\frac{P}{760}\right)\left(\frac{273}{273+T}\right)\left(\frac{100}{9(W)\%}\right)\left(O_2\right) = L/M^2/hr.$ where P is the barometric pressure during the experimental run, T is the average temperature of the chamber, W is the weight of the animal, L represents liters, and M^2 represents square meters of body surface. In correcting to standard temperature and pressure, the change in room temperature was considered to be negligible.

To establish control values for oxygen consumption and body temperature, 40 unoperated Sprague-Dawley rats and 16 "sham operated" rats, fasted for 16 to 18 hours, were tested in the above mentioned apparatus.

Thirty-four rats, surviving hypothalamic lesions made with the stereotaxic instrument, were selected for the experimental group on the basis of appearance, feeding habits, and growth. The animals with lesions were allowed to recover from the operative procedure for about seven days before they were tested. Before and during the recovery period the animals were kept in a room the temperature of which was maintained at 81° F.

Each animal, control or experimental, was tested only once. The entire group of tests extended over a two year period. Alterations in oxygen consumption and body temperature due to seasonal influences were thus obviated.

Upon completion of an experiment the rat was killed by an overdose of ether and perfused with 10 per cent formalin. Its brain was removed, fixed, dehydrated, imbedded in paraffin, and sectioned at 15 microns from the midsagittal plane outward. Every tenth section from each half of the brain was mounted and stained by the cresyl violet technic of Tress and Tress;[11] adjacent sections were stained by the technic of Weil.[12]

RESULTS

Mortality of the operated rats during the recovery period was about 60 per cent. It was found that the animals which subsequently died refused to eat and progressively lost weight, a loss of 40 to 60 gm. proving fatal. Feeding soft, wet laboratory chow, forced feedings, antibiotic treatments, or saline and glucose injections did not protect against this high mortality rate, nor did treatments with ACTH or adrenal cortex extract.

The average oxygen consumption rate for normal and sham operated control rats was 25.2 $L/M^2/hr$. Their body temperatures averaged 37.2° C. at zero minutes and manifested gradual decreases to an average of 34.6° C. toward the end of the stress period. These values were used as the base line with which the oxygen consumption rates and body temperatures of the experimental animals were compared (figures 1, 2, 3, 4).

The physiologic data found in experimental animals fell into four groupings with regard to oxygen consumption rates and body temperatures. His-

TABLE 1

DEGREES OF DAMAGE TO SPECIFIC STRUCTURES IN RATS WITH LESIONS IN THE POSTERIOR PART OF THE HYPOTHALAMUS (GROUP 1)

Animal No.	*Posterior hypothalamic area*	*Lateral and medial mammillary nuclei*	*Fornix*	*Lateral hypothalamic area*	*Mammillothalamic tract*	*Periventricular system*	*Supramammillary area*
520	xx	xxx	xxx r	x r	xx	x	xxx
558	xxx	x	x	xxx	xx	xx	xxx
570	xxx r	o	o	xxx r	xx r	xx	xxx
L-5	xxx	o	o	x	o	x	xx
L-3	xxx	o	o	x	o	x	o
L-1	xxx	o	o	xx	o	x	xx
M-10	xx r	o	o	xx	o	x	xxx r

o — no damage; x — slight damage; xx — moderate damage; xxx — extensive damage; r — more damage on right side; l — more damage on left side

tologic examination showed that the physiologic groups could be correlated with relatively specific sites of lesions in the hypothalamus. The first group, consisting of seven animals, displayed an average oxygen consumption rate about 58 per cent higher than the controls (figure 1). During the stress period, the oxygen consumption rate of this group started at 42.5 L/M²/hr., fell sharply to 35.2 L/M²/hr., then gradually rose again to 38.4 L/M²/hr., and finally fell slowly to a level of 37 L/M²/hr. The average overall rate was 38.2 L/M²/hr. The average body temperature of this experimental group remained slightly higher than that of the control group throughout the stress period. It was initially at 37.2° C. and then fell gradually to 35.8° C. which was slightly more than one degree higher than that of the control group. The lesions in this group of rats were found to be situated in the posterior hypothalamus where they occupied the supramammillary area, the areas of the medial and lateral mammillary nuclei, and sometimes the extreme posterior and lateral areas of the hypothalamus (figure 5). Specific hypothalamic damage to individual rats is given in table 1.

In the second group, consisting of ten animals, low oxygen consumption and marked fall in body temperature were typical. During the stress period there occurred a slight rise in average rate of oxygen consumption from an initial 10 L/M²/hr., followed by a temporary leveling off at 11.2 L/M²/hr., and this in turn was followed by an increase to a terminal level of 13.5 L/M²/hr. The overall average for the two and one-half hours of stress was 11.8 L/M²/hr., which represented a 53 per cent lower oxygen consumption than that of the control rats. Along with this extremely low oxygen consumption rate there was a marked fall in body temperature, from 35.8° C. to 28° C. during the 150 minutes of cold stress (figure 2). Animals in this group had dorsal tuberal lesions with damage to the dorsal and medial nuclear area extending downward to but not including the ventral medial nucleus. The middle portion of the lateral tuberal area also was involved (figure 6). In

TABLE 2

DEGREES OF DAMAGE TO SPECIFIC STRUCTURES IN RATS WITH LESIONS IN THE DORSAL AREA OF THE TUBERAL HYPOTHALAMUS (GROUP 2)

Animal No.	*Dorsal hypothalamic area*	*Dorsomedial nucleus*	*Ventromedial nucleus*	*Arcuate periventricular nucleus*	*Median eminence*	*Lateral hypothalamic area*	*Fornix*
M-5	xxx	xxx	x	o	o	xx	x
586	xxx	xxx	xx	x	o	xx	xx
584	xxx	xx	o	o	o	xxx	o
556	x	xxx	x	x	o	xxx	xxx
548	x	xxx l	xx l	xx	o	xxx	xx
524	xxx	xx	x	o	o	xxx	x
542	xx r	x r	o	o	o	xx	o
522	xxx	x	o	o	o	xx	x
K-12	xx	xx	x	o	o	xx	o

Key to symbols same as for table 1.

these animals it was noted that in all cases the dorsal hypothalamic area including the dorsomedial nucleus and the lateral hypothalamic area were extensively damaged (table 2). The periventricular nucleus, median eminence, and ventromedial nucleus were rarely involved and then only slightly.

There were 12 animals in the third group. These animals did not demonstrate any observable alterations in oxygen consumption or body temperature. Their average oxygen consumption rate started at 26.1 L/M²/hr., dropped gradually to 22 L/M²/hr., rose slightly to 23.8 L/M²/hr., and then fell to 21.7 L/M²/hr. at the end of 150 minutes of cold stress. The average for the test period was 23.4 L/M²/hr., which was little different from the 25.2 L/M²/hr. average of the controls (figure 3). Their body temperatures started at 36.2° C., then fell gradually throughout the experiment to 33.9° C. after 150 minutes of stress. Lesions in these animals were found in the ventral tuberal hypothalamus involving the area of the ventromedial nucleus and the arcuate periventricular nucleus (figure 7, table 3).

In the fourth group, which included seven animals, the oxygen consumption rates of the animals during the first 90 minutes of cold stress remained within the range of the controls, starting at 22.4 L/M²/hr. and rising to 25 L/M²/hr., then falling to 24.2 L/M²/hr. After 90 minutes it decreased steadily to an average level of 20.9 L/M²/hr. at 150 minutes (figure 4). It should be noted especially that even though oxygen consumption rates remained normal for the initial 90 minutes of stress, these animals appeared to lose their ability to increase metabolism as indicated by the fact that their temperatures fell steadily from the beginning of the experiment (35.8° C. initially to 28.6° C. after 150 minutes of cold stress). These animals were found to have lesions in the anterior hypothalamus involving the suprachiasmatic nucleus, diffuse supraoptic nucleus, and part of the medial portion of the lateral area of the

TABLE 3
DEGREES OF DAMAGE TO SPECIFIC STRUCTURES IN RATS WITH LESIONS IN THE VENTRAL AREA OF THE TUBERAL HYPOTHALAMUS (GROUP 3)

Animal No.	*Dorsal hypothalamic area*	*Dorsomedial nucleus*	*Ventromedial nucleus*	*Arcuate periventricular nucleus*	*Median eminence*	*Lateral hypothalamic area*	*Fornix*
552	o	o	xxx	xxx	o	xx	o
560	o	x	xxx	xxx	o	xx	o
566	o	xx	xxx	xxx	o	xxx	o
572	o	o	xxx	xxx	o	x	o
574	x	xx	xxx	xxx	o	xxx	o
578	o	o	xxx	xxx	o	o	o
580	o	o	xxx	xxx	o	o	o
K-10	o	o	xxx	xxx	o	o	o
K-9	o	o	xx	xx	o	xx	o
L-8	x	xx	xx	xx	o	xx	o
L-4	o	o	xxx	xxx	o	x	o
L-2	o	xx	xx	xx	o	x	o

Key to symbols same as for table 1.

hypothalamus. In none of the animals of this group were the lesions found to extend into the preoptic area (figure 8, table 4).

DISCUSSION

The findings in the first group of rats, those with posterior lesions showing high oxygen consumption rates and relatively normal body temperatures (figure 1), agree with the results of Clark, Magoun, and Ranson[13] who have shown that cats with bilateral lesions in the caudal part of the lateral hypothalamus have severely impaired abilities to prevent either overheating or chilling but that the medially placed lesions do not impair this ability. It was found by comparison of their lesions, which produced poikilothermia in cats, with our posterior lesions in rats (figure 5) that our lesions were more medially and somewhat more caudally placed. It is possible that had oxygen consumption rates been measured by Clark, Magoun, and Ranson they would have found a high metabolism in those animals with medially placed lesions.

The observations in our second group of rats, those with dorsal tuberal lesions demonstrating low oxygen consumption rates and lowered body temperatures while in a cold environment (figure 2), compare favorably with the findings of Clark, Magoun, and Ranson who also demonstrated that bilateral lesions of the lateral hypothalamus result in moderately impaired ability to prevent chilling. Their lesions were similar to the ones found in our animals (figure 6), and it is possible that the oxygen consumption rates in their animals would have been low, had they been measured, because the body temperatures in their animals fell. Hetherington and Ranson,[14,15] studying the

TABLE 4

DEGREES OF DAMAGE TO SPECIFIC STRUCTURES IN RATS WITH LESIONS IN THE ANTERIOR PART OF THE HYPOTHALAMUS (GROUP 4)

Animal No.	*Anterior hypothalamic area*	*Reuniens nucleus of thalamus*	*Lateral hypothalamic area*	*Supra-chiasmatic nucleus*	*Diffuse supraoptic nucleus*	*Peri-ventricular system*
522	x	0	x	xxx	xxx	x
526	xxx	x	xxx	x	0	x
554	xx	x	xx	xxx	xxx	x
562	xx	x	xx	xxx	xxx	x
568	xx	0	xx	xxx	xx	x
582	xx	0	xxx	xx	xxx	x
L-6	xx	0	x	xx	xxx	x

Key to symbols same as for table 1.

phenomenon of adiposity, found that oxygen consumption was low in obese rats when compared to the controls; however, they did not state with certainty whether their animals had subnormal body temperatures. Had they studied body temperatures and found them low, this would not be incompatible with our findings in this group of animals. Adiposity developed rapidly in the animals Hetherington and Ranson investigated and it was found that their lesions largely involved the ventromedial nucleus of the hypothalamus. However, the lesions in this group of our animals mainly involved the dorsomedial nucleus of the hypothalamus and thus accounted for the differences between their animals and ours. As far as could be determined, our animals did not have an abnormally high weight gain during the period of examination and testing, although that period of time was insufficient for the development of obesity.

The findings in our third group of rats, which had lesions occupying the ventral tuberal region of the hypothalamus (figures 3, 7) and which showed no observable deviation from normal of either oxygen consumption rate or body temperature, are supported by the experimental work of Keller[16] who found that, when the ventral two-thirds of the hypothalamus were removed either bilaterally or unilaterally, temperature regulation was not impaired. It was only when the dorsal one-third of the hypothalamus was encroached upon bilaterally that a loss of temperature regulation could be demonstrated.

McCrum[17] has shown, in cats with electrolytic lesions in the anterior hypothalamus, that the heat loss and heat conservation mechanisms seem to be located in the anterior hypothalamus and the preoptic area in a diffuse manner with distribution and extent varying from cat to cat. Animals with lesions in the anterior hypothalamus and preoptic area were found to have subnormal body temperatures at room temperature. Our research lends support to the results observed earlier by McCrum.

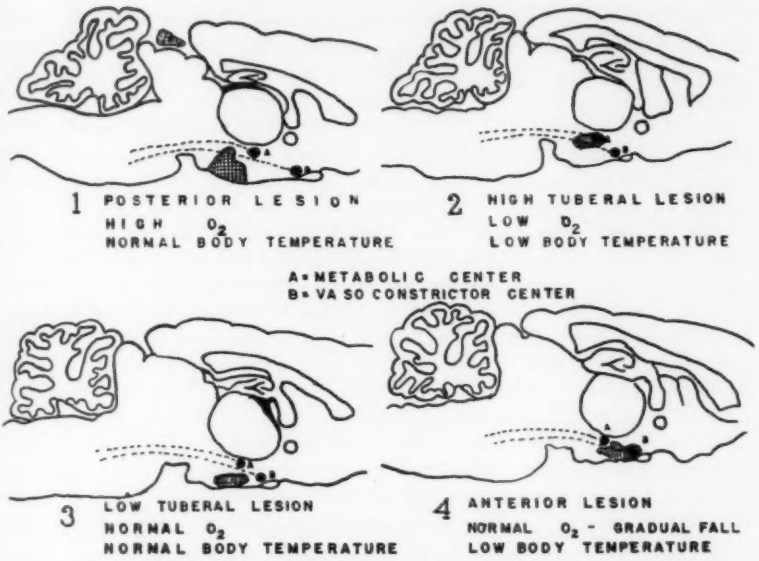

FIG. 9. Diagram of parasagittal rat brain sections to indicate possible locations of the vasoconstrictor and metabolic centers within the hypothalamus, as suggested by the experimental observations and theoretical implications of such lesions so far as functions of the centers are concerned.

The lesions around the optic chiasm in the fourth group of rats suggest interference with the vasoconstrictor mechanism, as evidenced by immediate fall in body temperature, but probably did not directly damage the metabolic mechanism because oxygen consumption did not begin to fall after 90 minutes of stress (figures 4, 8). If the vasoconstrictor mechanism is nonfunctional it would appear that the blood is chilled rapidly, resulting at first in a stimulation of the metabolic mechanism, followed as the blood is progressively cooled by a blocking effect similar to the course of events postulated by Barbour, McKay, and Griffith.[9]

No direct observations were made on the degree of vasoconstriction in our experimental groups; however, the existence of a vasoconstrictor mechanism has been established by the literature. Barbour, McKay, and Griffith[9] attributed water shift, under cold stress, from the periphery of the body to cells of visceral organs partially to peripheral vasoconstriction controlled by the anterior hypothalamus. Pembrey,[18] Bazett,[7,8] Magoun, Harrison, Brobeck, and Ranson,[19] Folkow, Strom, and Uvnas,[20] and Hardy[21] also subscribe to the existence of a vasomotor center within the hypothalamus. We believe that vasoconstriction was eliminated as a factor in temperature regulation in our animals with lesions in the anterior hypothalamic area. Our experimental observations indicate activity of separate vasoconstrictor (heat conservation) and metabolic (heat production) mechanisms in the hypothalamus.

We believe that our results, which are supported in part by the literature, suggest that certain lesions of the hypothalamus may account for alteration in muscular activity which is manifested by abnormal metabolic adjustments when animals are subjected to cold stress. Although no direct observations could be made on the animal's motor activity while under cold stress, it was observed that those animals with high or normal oxygen consumption rates, normal body temperatures, and ventral tuberal or posterior hypothalamic lesions shivered violently when removed from the chambers after the stress period. On the other hand, those animals having low oxygen consumption rates, low body temperatures, and dorsal tuberal lesions were extremely inactive and somnolent on termination of the experiment. The importance of muscular activity in increased heat production is emphasized in the literature by Pembrey,[18] Keller and Hare,[22] Bazett,[7,8] and Burton and Bronk.[23] All these investigators agree that muscular activity plays an important role in heat production under cold stress conditions. When anesthetized cats were placed in a 35° C. environment, Burton and Bronk observed intermittent and uncoordinated muscular twitches which were coincident with the first signs of a rise in oxygen consumption. When the twitches developed into gross tremor an extremely high oxygen consumption had been reached. Bazett[7] states: "Reflex shivering or other reflex increases in movement probably constitute the chief methods by which the metabolism is increased in response to cold."

The above discussion is not enough to explain all the reactions observed in the four experimental groups. A discrepancy appears when the oxygen consumption rate and body temperatures in animals with anterior lesions are compared with those in animals having posterior lesions. The divergent results in these two groups may be interpreted as indicating the existence of another mechanism in the posterior hypothalamus tentatively presumed to be an inhibitory system influencing the metabolic center. A drop in body temperature in the group with anterior lesions was accompanied by an oxygen uptake which was only one-half to two-thirds that in the group with posterior lesions. The degree of superficial vasoconstriction was not determined but it may be assumed, because of damage to the vasoconstrictor center as located by previous investigators, to be relatively small. The most likely explanation of the unexpectedly high oxygen consumption rate in the animals with posterior lesions is the existence of an inhibitory system which influences the metabolic center and which is, at least partially, destroyed by the posterior lesions.

In rats with dorsal tuberal hypothalamic lesions, neither the vasoconstrictor center nor the metabolic center seemed functional (figure 2). Because of sharp reductions in body temperatures and extremely low oxygen consumptions, it is postulated that the heat conservation (vasoconstrictor) mechanism is seriously damaged and therefore fails to respond in the normal way to the stimulation of the cold external environment, and also that damage to the metabolic mechanism prevents it from responding to the cold stimulus in animals with dorsal tuberal hypothalamic lesions. Of the two mechanisms probably responsible for the regulation of body temperature, that mechanism pro-

ducing heat seems to be the more important. The second mechanism, vasoconstriction effected by a vasoconstrictor center, seems to be able to alter the reaction to cold to only a moderate extent.

A comment should be made on the high mortality rate observed in our stocks of experimental animals. This is explainable on the basis of the work of Clark, Magoun, and Ranson[13] who found that large hypothalamic lesions usually were fatal, and on that of Anand and Brobeck[24] who located a "feeding center" in the lateral area of the hypothalamus, near the ventromedial nucleus, which, if destroyed, causes the animals to die of starvation. The 60 per cent mortality rate observed in our experimental animals with large lesions supports these conclusions.

The physiologic results observed and the locations of the lesions, as determined from serial sections of the brains of our experimental animals, support but do not prove the hypothesis that centers concerned with heat conservation are located in the suprachiasmatic region of the hypothalamus, in close proximity to the optic chiasm, and that there is a heat production center in the midtuberal area near the ventral limits of the thalamus.

SUMMARY

By means of a newly devised stereotaxic instrument, lesions were placed in various areas of the hypothalami of Sprague-Dawley albino rats with electrodes which traversed the brain from side to side in the horizontal plane. Such lesions resulted in a high mortality rate and produced various hypothalamic syndromes in many surviving animals.

Upon evaluation of the physiologic and anatomic data it was found that the operated animals fell within four groups:

1. Animals with posterior hypothalamic lesions showed a high oxygen consumption rate and a relatively normal body temperature.

2. Animals with dorsal tuberal hypothalamic lesions demonstrated low oxygen consumption rates with low body temperatures.

3. Animals with ventral tuberal hypothalamic lesions did not exhibit any change in oxygen consumption rates or body temperatures.

4. Animals with anterior hypothalamic lesions showed gradual falls in oxygen consumption rates and a concomitant gradual lowering of body temperatures.

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Great as is the aid which, during the last twenty years, the microscope has afforded in the investigation of the structural changes which underlie or constitute many diseases of the nervous system, it cannot be said to have thrown much light on the nature of idiopathic epilepsy. Of the minute histological changes which have been described, most, if not all, of those which are not common to many other diseases, are apparently secondary changes, the result and not the cause of the violent functional disturbance, or the effect of the repeated passive congestion to which the organs have been exposed. Such are the increased size of the blood-vessels of the medulla oblongata, described by Schroeder van der Kolk; the distention of the perivascular sheaths with pigment, the relics of former extravasations; and the yellow pigmentation of the nerve-cells of the medulla described by Voisin.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

Functional Organization of the Central Nervous System

With Respect to Orientation in Time

John Campbell, M.D.

AT ALL LEVELS of development a major function of the central nervous system is to orient the individual in his environment. On the basis of the present concept of reality as a space-time continuum, time is considered one dimension of our environment. If this concept is used to examine the functional organization of the nervous system, some interesting facts come to light, and one can arrive at a simplification of the central nervous system's functional organization. Furthermore, some clinical facts are more easily explained.

No attempt will be made here to throw light on psychologic mechanisms, personality structure, mechanisms of memory, intellect, or neurophysiologic observations, but it is intended to point out the clear and simple organization of the brain with reference to orientation in our environment, which now includes time as one dimension.

The basic sensorimotor organization of Hughlings Jackson[1] is too much a part of our present idea of the central nervous system to need further discussion. One basic proposition will have to be accepted, that is, that motor activity can only occur in the immediate future and sensory response only in the past. There is no absolute present, only a constant changing process correlating the past and future.

In figure 1 the spinal cord is represented diagrammatically. Directing attention only to the gray matter, motor function is represented anteriorly; vegetative control is in the midline; sensory experience is posterior. The response of the isolated cord is immediate. The activity of the motor (anterior) area is considered to be future in time and the sensory, past. Progressing up the neural axis this sensorimotor and visceral organization is strictly adhered to, including all the subcortical structures. The basal ganglia (extrapyramidal system) are primarily motor, the thalamus primarily sensory. The midline structures of the thalamus and hypothalamus are vegetative motor and sensory diencephalic centers. The response of all subcortical structures is immediate with respect to orientation in time.

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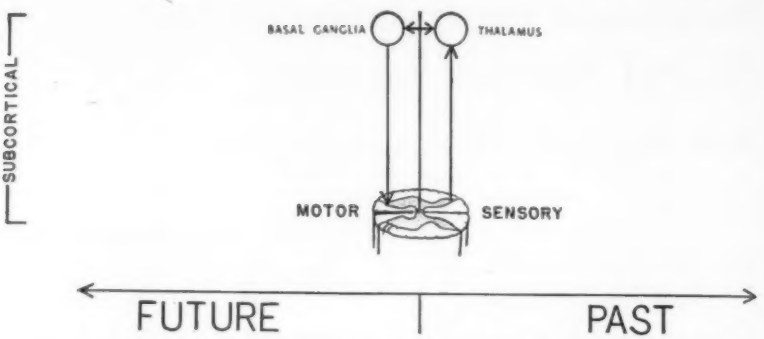

FIG. 1. "The response of all subcortical structures is immediate with respect to orientation in time."

Progressing to the cortex, discrimination is met with for the first time. Initiation of movement or primary sensory experience can enter consciousness below the cortex, but the cortical layers can be considered as discriminatory in function. Phylogenetic, embryonic, and myelogenetic studies of cortical development reveal that the frontal and inferior temporal-occipital cortices are the last to develop. Flechsig's myelogenetic contributions to development of the cortex (figure 2) make this point most apparent.[2] Furthermore, the appearance of adult electroencephalographic activity occurs late in the temporal-occipital cortex. In brief, the brain develops both anteriorly and in the direction of the temporal-occipital cortex as shown in figure 3. The cortical architectural studies of Bailey[3] disclose only four primary areas: the alocortex, motor or pyramidal cortex, sensory or granular cortex, and the isocortex. Finally, organization of the cortex is the same as subcortical structures, that is, the motor in the anterior cerebrum, visceral in the midline, and sensory in the posterior cerebrum.

Reference is made to figure 4 where the frontal lobes are first to be considered. In the precentral gyrus, simple discriminative movement is initiated, or movement in the immediate future. Progressing anteriorly simple discriminative movements are organized, associated into purposeful activity which requires planning in the immediate future (eupraxia). This is in large a function of the dominant hemisphere. Still farther anteriorly and demanding both hemispheres intact, there are located the areas for concrete discrimination of the remote future, that is, concrete planning ability, planned initiative, evaluation of the future on a concrete level.[4]

Finally reaching the prefrontal poles (areas 9 and 10) abstract discrimination of the future is located. By abstract is meant the individual's general image of his own future activity. It has been recently pointed out by Freeman[5] that following prefrontal lobotomy the patient's abstract concept of himself continuing in the future has been destroyed. Denny-Brown[6] con-

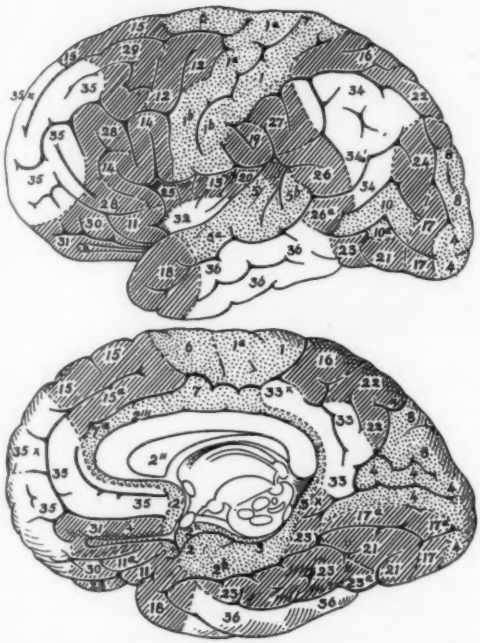

FIG. 2. Order of myelogenetic development of the cortex, from Flechsig.

siders the deficit following lobotomy as "abstract, projected in time and space, and directly concerned with visualizing motor and affective resultants. The whole future setting fails to resolve as a stimulus for an act." The rest of the personality and the central nervous system function is unimpaired as far as can be determined by elaborate testing methods. Clinically the deficit is obvious.

Cortical representation of emotional function is represented in the midline, both in the motor and sensory sphere, as shown in the middle of figure 4. The orbital gyri, and anterior cingulate gyri have been related to affect; the posterior cingulate and the temporal pole have been described as being important in emotional feeling.[7–10] Emotional expression and feeling are immediate responses and are not involved in the concept of time, but they are responsive to past and future orientation.

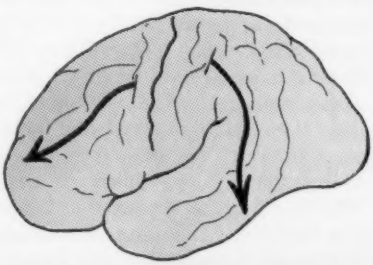

FIG. 3. Cortical development occurs anteriorly and in the direction of the temporal-occipital cortex.

In the posterior cerebrum, a similar localization is found to be present,

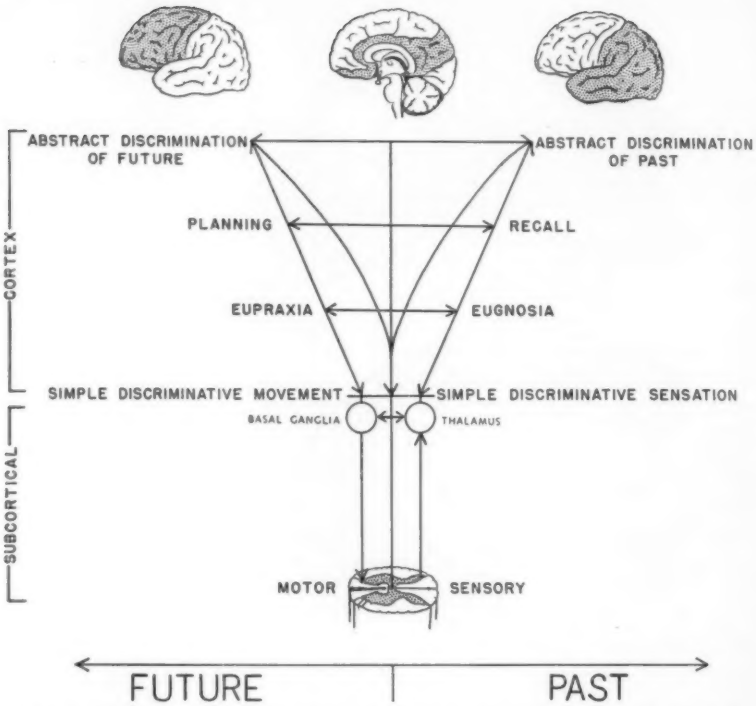

FIG. 4. Schema of the functional organization of the central nervous system with respect to orientation in time.

if one considers the parietal, occipital, and temporal lobes as one structure. Simple discriminative sensations arise from the primary sensory cortical areas, the granular cortices of the postcentral gyrus, the calcarine fissure, and the transverse gyrus of Heschl. In the cortex surrounding these areas in the parietal lobe and first temporal convolution organization of sensation takes place, the dominant hemisphere being primarily involved in the function of eugnosia (concrete organized recognition of the immediate past). It has been shown by Penfield[11] in studying epileptic foci that recall of past experience results from stimulation of the parietotemporal cortex (figure 5). Recall, in this case called memory by Penfield, is concrete discrimination of the remote past. This is a function represented bilaterally. Now entering areas 20 and 21 on the lateral and inferior surface of the temporal lobe, abstract discrimination of the past is postulated; this is a purely speculative concept. This area is the latest to develop, as has been previously mentioned, and is related to areas 9 and 10 through rich association pathways, the uncinate and arcuate fasciculi.

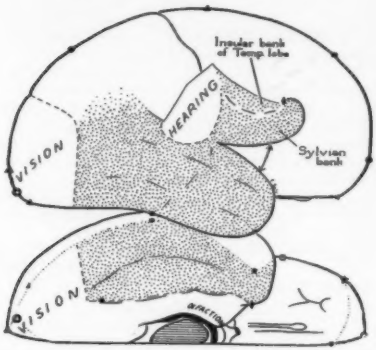

FIG. 5. Penfield's studies[11] disclose that recall of past experience results from stimulation of the parietotemporal cortex (shaded area).

This concept implies that the central nervous system functions as a whole, with focal areas carrying out special functions. Memory, intellect, consciousness, and personality aspects have not been considered; these are functions of the entire cerebrum. Memory is to be differentiated from recall or recollection.

The advantages of this approach to the central nervous system are: 1) it simplifies the concept of the functional organization; 2) a framework for psychologic mechanism is presented; 3) explanation is given for the effects of hypnosis, hypnotic drugs, shock therapies, and prefrontal lobotomies, all of which either temporarily or permanently focus the individual's image of himself to the immediate; 4) it leads to an interest in the inferior temporal-occipital cortex, as yet an area of unknown function. Studies of this cortex are in progress.

SUMMARY

If the modern concept of reality, a relative space-time continuum, is used as the basis for considering the primary central nervous system function of orientation, one arrives at an interesting and simplified concept of the brain. Using the basic sensorimotor organization of the central nervous system, and assuming that motor function can only occur in the future, sensory experience only in the past, the organization of the cerebral cortex (a discriminative organ) can be divided into past and future orientation. The midline cortex ("visceral brain") is not concerned with orientation in time. The value of this different approach is discussed.

The author wishes to thank Dr. A. R. Vonderahe for his guidance. Appreciation is also expressed to Dr. F. S. C. Northrop of Yale University for his constructive criticism of the basic concept of this paper.

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Todd taught that the "epileptic hemiplegia" was due to exhaustion of part of the brain by the excessive action, and the same theory has been accepted by Hughlings Jackson and by A. Robertson of Glasgow. The former has suggested that the weakness and foot-clonus may be the result of the exhaustion of the fibres of the internal capsule of the brain or lateral columns of the cord by the "discharge" through them, since in organic disease the occurrence of this symptom is especially related to sclerosis of these columns. The hypothesis affords a very probable explanation of some of the weakness after very severe fits, and of the excess of myotatic irritability in these cases; and the loss of the knee-jerk, which is found immediately after some fits, may be due to the initial exhaustion of the lumbar centres of the cord. But it is not easy to explain on this theory all the phenomena of post-epileptic paralysis. It is difficult to explain as an effect of "exhaustion" the extreme weakness which may exist in the arm, and occasionally in the leg, after a slight local fit. The difficulty is increased if we regard the exhaustion as affecting chiefly the nerve fibres, which are not readily exhaustible to the extent of causing such loss of power as is sometimes observed. There is also a disproportion between the severity of the fit and the subsequent paralysis. A patient may have a severe general convulsion, and, a few minutes later, may have no conspicuous weakness, while another patient, who has had a fit confined to one arm, apparently slight in degree, may be unable to move the limb for an hour or more. Dr. Jackson has suggested, as an explanation of this discrepancy, that the sudden violent discharge is diffused widely, overcoming widely the resistance, by its force; while the slower local discharge, having more "momentum," does not diffuse itself, is concentrated on certain parts, which are thus stimulated for a longer time and in greater absolute degree, and so become exhausted. But there is no evidence that a slight discharge of long duration exhausts the nerve elements more than a severe but brief discharge. Moreover, a comparison of a series of cases shows that there is no relation between either the duration or degree of convulsion, or both, and the subsequent weakness.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

TREATMENT REVIEW

This section is designed to give prompt publication to the results of reliable studies in therapy, to record newer methods of treatment, and to encourage research in therapy of neurologic disorders.

AUGUSTUS S. ROSE, M.D., *Section Editor*

Present Concepts in the Treatment of Purulent Meningitis

John W. Hanbery, M.D.

DURING the past ten years, the treatment of purulent meningitis has undergone many changes. The mortality rate has been gradually lowered for all types of pyogenic meningitis, and the majority of patients now recover from this formerly fatal illness. The results of therapy, however, are still far from optimal. There remain unnecessary deaths as well as an increasing number of survivors with disabling sequelae, resulting from delayed clinical and bacteriologic diagnosis and inadequate antibiotic therapy.

Most of the available antibiotics have now undergone sufficient experimental and clinical investigation so that an evaluation of their use in the treatment of purulent meningitis can be made. It is necessary to know something of the physical properties, antibacterial activity, and inherent dangers of each of the antibiotics if they are to be used wisely and effectively.

ANTIBIOTICS

*Penicillin**

Penicillin remains the most widely used antibiotic in the treatment of purulent meningitis, being effective against most gram-positive organisms and some of the gram-negative bacteria. Except for rare allergic manifestations the drug has no general toxic effects even when given parenterally in high dosage. Many investigators[1–4] have reported the absence of significant levels of penicillin in the spinal fluid, even in cases of meningitis, when the average intravenous or intramuscular doses have been given over a period of hours or days. It was this finding that led to the early use of penicillin intrathecally. More recently, several workers[2,5,6] have shown that bacteriocidal penicillin levels can be rather quickly produced and maintained by large doses of 0.5 to 1 million units given intravenously or intramuscularly every two to three hours.

Both experimentally[7–9] and clinically[10–15] penicillin has been found to be an irritant when injected into the cerebrospinal fluid. Pleocytosis and signs of meningeal irritation have occurred after even small intrathecal injections. Ad-

*Crystalline penicillin 1,600 units = 1 mg.

From the department of neurology and neurosurgery, McGill University, and the Montreal Neurological Institute, Montreal. Reprint No. 453.

TABLE 1
SUMMARY OF THERAPEUTIC AGENTS IN TREATMENT OF PURULENT MENINGITIS

Sensitive organisms	*Dose*	*Possible toxicity*
PENICILLIN		
N. meningitidis D. pneumoniae Strept. pyogenes Staph. pyogenes	*Intramuscular:* 0.5–1 million units every 2–3 hours for 48–72 hours; then 500,000 units every 8 hours. Meningococcal meningitis usually requires only 1 million units twice daily. *Intrathecal:* (adult) 20,000 units in 10 cc. of isotonic saline. (child) 5,000–10,000 units in 5 cc. of isotonic saline. *Intracisternal:* 5,000–10,000 units in 10 cc. saline. *Intraventricular:* 10,000 units in 10 cc. of saline.	*Systemic* dermatitis drug fever *Intrathecal* pleocytosis arachnoiditis radiculitis myelopathy convulsions
STREPTOMYCIN		
H. influenzae D. pneumoniae Strept. pyogenes Staph. pyogenes Esch. coli Salmonellae Ps. aeruginosa Prot. vulgaris	*Intramuscular:* (adult) 0.5–1 gm. every 8 hours. (child) 40 mg./kg. in divided doses daily. *Intrathecal:* (adult) 50–100 mg., (child) 25–50 mg., in 5 cc. saline. *Intracisternal:* (adult) 50 mg., (child) 25 mg., in 5 cc. saline. *Intraventricular:* Same as for intrathecal.	*Systemic* dermatitis drug fever nausea vertigo ataxia tinnitus deafness *Intrathecal* pleocytosis radiculitis convulsions coma
BACITRACIN		
D. pneumoniae Strept. pyogenes Staph. pyogenes	*Intramuscular:* (adult) 10,000–25,000 units every 4 hours. (child) 400 units/kg. every 6 hours. *Intrathecal:* (adult) 5,000–10,000 units in 10 cc. saline. (child) 500–3,000 units in 5–10 cc. saline. *Intraventricular:* (adult) 5,000 units in 10 cc. saline. (child) 250–1,000 units in 10 cc. saline.	*Systemic* malaise drug fever headache renal damage *Intrathecal* pleocytosis radiculitis convulsions
CHLORAMPHENICOL		
H. influenzae N. meningitidis D. pneumoniae Strept. pyogenes Staph. pyogenes Esch. coli Salmonellae Prot. vulgaris	*Oral:* (adult) 1–2 gm. initial followed by 750 mg. every 6 hours. (child) 750 mg. initial followed by 250 mg. every 4 hours. *Intramuscular:* 100 mg./kg. daily. *Intravenous:* same as intramuscular. *Intrathecal:* 5 mg. in 5 cc. of isotonic saline. *Intraventricular:* same as intrathecal.	*Systemic* nausea diarrhea stomatitis headache dizziness granulocytopenia *Intrathecal* none known
AUREOMYCIN		
H. influenzae N. meningitidis D. pneumoniae Strept. pyogenes Staph. pyogenes Esch. coli Salmonellae	*Oral:* (adult) 500 mg. every 6 hours. (child) 15 mg./kg. every 6 hours. *Intravenous:* (adult) 500 mg. every 12 hours. (child) 7 mg./kg. every 12 hours.	*Systemic* nausea vomiting diarrhea dermatitis stomatitis *Intrathecal* not injected
TERRAMYCIN		
H. influenzae N. meningitidis D. pneumoniae Strept. pyogenes Staph. pyogenes Esch. coli Salmonellae	*Oral:* (adult) 1 gm. initially followed by 500 mg. every 4 hours. (child) 10 mg./kg. every 4 hours. *Intravenous:* (adult) 500 mg. every 12 hours. (child) 250–500 mg. every 12 hours.	*Systemic* nausea vomiting diarrhea dermatitis stomatitis *Intrathecal* not injected

TABLE 1—(continued)

POLYMYXIN B

Sensitive organisms	*Dose*	*Possible toxicity*
H. influenzae Esch. coli Salmonellae Ps. aeruginosa	*Intramuscular:* (adult) 2.5 mg./kg. in 4 divided doses. Maximum daily dose of 200 mg. (child) 2.5 mg./kg. in 4 divided doses. *Intrathecal:* (adult or older child) 5 mg. in 2 cc. distilled water daily for 3–4 days then every 2 days. (infants) 2 mg. in 2 cc. distilled water daily for 3–4 days then 2.5 mg. every 2 days.	*Systemic* malaise headache drug fever paresthesias renal damage *Intrathecal* pleocytosis neck stiffness hypotonia of legs

hesive arachnoiditis, root pain, difficulty in voiding, and transverse myelopathy have been reported[8,11] in patients after injection of no more than 50,000 units. Injections into the cisterna magna of 40,000 to 50,000 units have led to convulsions, coma, and death.[1] In animals, the injection of as little as 500 units/cc. of penicillin into the cortex has caused the appearance of electrographic spike potentials and seizures.[7]

While some authors[15,16] continue to use relatively high doses of intrathecal penicillin of 50,000 to 100,000 units, most workers[8,17,18] now feel that 20,000 units is the maximal intrathecal dose for an adult, and that no more than 10,000 units should be injected intraventricularly or intracisternally (table 1). This dose should be mixed in 10 cc. of normal saline and injected slowly after an equal amount of spinal fluid has been withdrawn. For infants and small children 5,000 to 10,000 units in 5 cc. of saline is the recommended intrathecal dose. Doses of this magnitude will maintain an effective bacteriocidal level in the cerebrospinal fluid for a period of 24 hours.[19]

At the present time there is a definite trend in favor of higher doses of intramuscular penicillin and away from frequent intrathecal injections. Some would give up intrathecal penicillin entirely; most, however, continue this method using moderate doses for one to four days depending on the organism, together with high doses of 2 to 12 million units intramuscularly daily.

*Streptomycin**

The development of this drug with its bacteriocidal action against many of the gram-negative and a few of the gram-positive organisms was a great advance in the treatment of purulent meningitis, and it has become the basis of treatment in tuberculous meningitis. In the recommended doses of 0.5 to 1 gm. intramuscularly every eight hours for adults and 40 mg./kg. intramuscularly daily in divided doses in children, streptomycin produces a variety of toxic manifestations in a few people (table 1). Such phenomena as headache, nausea and vomiting, and skin eruptions are annoying but not dangerous. Neurotoxic symptoms such as vertigo, tinnitus, ataxia, and impaired hearing are more serious. Fortunately, these do not usually occur unless streptomycin therapy is prolonged over two or three weeks. Hearing loss usually remains permanently.

The intramuscular injection of streptomycin fails to produce significant levels of the drug in the spinal fluid,[20] and intrathecal therapy must be employed. Both experimentally[21–24] and clinically,[25] streptomycin is epileptogenic when applied to the cortex, with a threshold of 100 to 200 mg. per cc. Pleocytosis[9,20,26] almost invariably follows intrathecal injection of this drug. Respiratory arrest and death have occurred in a patient[25] following intracisternal injection of 50 mg., and radicu-

*Streptomycin 1,000 units = 1 mg.

litis, paraplegia,[27] and coma[28] have been reported following intrathecal and intraventricular administration.

The usual intrathecal dose employed is 100 mg. daily in adults and 25 to 50 mg. daily for infants and children. The large number of cases of tuberculous meningitis receiving such doses over long periods of time has demonstrated that such a schedule is relatively safe. Adequate spinal fluid bacteriocidal levels can be maintained for 24 hours.

Because of the neurotoxic properties of streptomycin, the need for intrathecal administration, and the development of bacterial resistance, there is at present a definite trend away from the use of this drug in the treatment of certain gram-negative types of meningitis in favor of some of the newer antibiotics.

*Bacitracin**

This antibiotic, which was first described in 1945, is produced by a strain of *Bacillus subtilis* and has a wide antibacterial spectrum very similar to penicillin (table 1). This drug is frequently effective against streptococcal and staphylococcal infections which are resistant to penicillin. In some instances there seems to be a definite synergistic action between bacitracin and penicillin.

Oral administration of this drug fails to yield significant blood serum levels. The intramuscular injection of 10,000 to 25,000 units every four hours produces good blood levels but is often accompanied by toxic manifestations. Local pain at the injection site, fever, and malaise are sometimes observed, and in about 16 per cent of cases nephrotoxic signs appear with proteinuria and granular casts. Significant spinal fluid levels are not obtained following intramuscular injection, even when meningitis is present, and to be effective bacitracin must be injected intrathecally.

Both clinically and experimentally,[29,30] this drug acts as an irritant when injected into the subarachnoid space, and a pleocytosis is always observed. In animals, mild inflammatory changes occur in the meninges and degenerative changes are seen in the cord and nerve roots following cisternal injection of the drug. None of these changes are severe, and all seem reversible. Definite epileptogenic properties have been observed following direct application to the cortex of cats.[24]

Teng and Meleney[31,32] have had the largest experience with its clinical use. They report no untoward symptoms in 67 cases following repeated injections of 5,000 to 30,000 units in 5 cc. of saline via the subarachnoid, subdural, epidural, intracerebral, or intraventricular routes in various types of infection of the central nervous system. We have also had experience with the use of this drug and feel it is an important therapeutic agent in selected cases.

The greatest value of bacitracin lies in its use by intrathecal administration in those cases of streptococcal or staphylococcal meningitis which prove to be resistant to penicillin. It is not yet entirely safe to administer this drug intramuscularly. The intrathecal dosage recommended is 5,000 to 10,000 units in saline daily for adults, and 1,000 to 3,000 units in 5 cc. daily for infants and children.

Chloramphenicol

Chloramphenicol, known also as Chloromycetin, is one of the newer antibiotics which is formed by a soil actinomycete, *Streptomyces venezuelae*. It has been isolated in pure state and has been synthesized. It is a yellowish-white crystalline substance which is relatively insoluble and extremely stable. Concentrations of 2.5 mg./cc. can be obtained at room temperature. Solutions withstand boiling for five hours or autoclaving for 30 minutes without change in structure or loss of potency.[24,33]

This drug is a potent bacteriostatic

*Bacitracin 30 units = 1 mg.

agent against most of the gram-negative organisms as well as many of the gram-positive cocci (table 1). Of all the antibiotics, chloramphenicol diffuses most readily into blood and cerebrospinal fluid after oral administration.[34] Recommendations for oral dosage range from 50 mg./kg. to 200 mg./kg. daily in divided doses. In adults most clinicians have given 1 to 2 gm. as an initial dose followed by 750 mg. every six hours. Children usually receive 750 mg. initially, followed by 250 mg. every four hours. If vomiting occurs, a supplemental rectal dose, usually twice the oral dose, can be given every four hours. On such a regimen serum concentrations of 5 to 50 microg./cc. can be maintained.[34] Cerebrospinal fluid levels are rapidly produced over a period of a few hours and remain about one-half of the serum concentration. The drug can be given intravenously or intramuscularly in an organic solvent base in doses of 100 mg./kg. daily, but sometimes leads to local irritation at the injection site together with headaches, dizziness, nausea, and vomiting.

Chloramphenicol* was first given intrathecally with excellent results by Anderson and Ellis[33] in cases of staphylococcal meningitis resistant to penicillin and streptomycin. They found the injection of 750 microg. in 1 cc. of distilled water produced no untoward effect and, together with large oral doses, maintained a cerebrospinal fluid concentration of 40 microg./cc. for a period of 24 hours. During the past year we have employed this drug in doses of 5 to 20 mg. intrathecally and intraventricularly without clinical reactions.

Chloramphenicol was used in this fashion after it had been shown experimentally[24] that repeated daily cisternal injections of 1 mg. into cats failed to produce seizures, signs of meningeal irritation, or cord involvement; and, at the end of eight days the animals showed no gross or microscopic evidence of meningeal or parenchymatous reaction. Even when pure crystalline chloramphenicol was applied to the motor cortex, neither seizures nor electrographic spikes were observed over a period of nine hours. Animals surviving for one month after powdered chloramphenicol was placed over the sensorimotor cortex had no seizures or weakness, and histologic examination showed no significant reaction.

Nausea and vomiting are sometimes produced following the oral administration of this drug but can usually be minimized by giving it with food. Of far greater concern are the scattered reports of optic neuritis,[35] peripheral paresthesias,[36] and aplastic anemia[37,38] following the use of chloramphenicol. In most cases these serious reactions have occurred after prolonged ingestion of the drug, and in some cases a direct cause and effect relationship has not been completely established.

At the present time chloramphenicol is recognized as a potent antibiotic whose ease of administration and prompt diffusion into serum and spinal fluid makes it a particularly useful agent in the treatment of many forms of purulent meningitis.[39–45] The recent demonstration of the safeness of intrathecal injection adds greatly to the effectiveness of the drug. The circumstantial evidence of a possible relationship between serious neurotoxic symptoms as well as aplastic anemia and chloramphenicol demands definite indication for its use with avoidance of prolonged therapy beyond two to three weeks, but does not detract from its usefulness in selected cases.

*Pure crystalline chloramphenicol was used and not the powder dispensed commercially in capsule form.

Aureomycin

This antibiotic was discovered in 1948 and is elaborated by another actinomy-

cete, *Streptomyces aureofaciens*. It is prepared commercially by fermentation methods and is a golden yellow powder which forms an acid solution when dissolved. It has a broad antimicrobial spectrum being effective against most gram-positive and gram-negative organisms (table 1). Oral doses usually given are 500 mg. every six hours for adults and 15 mg./kg. every six hours in children. When mixed with a buffering solution of sodium glycinate, Aureomycin may be given intravenously 500 mg. every 12 hours for adults and 7 mg./kg. every 12 hours for children. Nausea, vomiting, diarrhea, stomatitis, and dermatitis occasionally follow oral administration. Taking the capsules with a glass of milk frequently prevents gastrointestinal complaints. Thrombophlebitis is a common sequela of intravenous administration.

Serum and cerebrospinal fluid concentrations of Aureomycin following oral administration are definitely lower than with chloramphenicol.[34] Aureomycin does diffuse into the spinal fluid when given by mouth, but requires 12 to 24 hours, is inconstant, and has no definite relationship to serum concentrations.[46–49]

Aureomycin has been given intrathecally and intraventricularly by Neter and co-workers[50] in one successfully treated case of meningitis due to *Aerobacter aerogenes* with no untoward effect. When this drug was applied directly to the cortex of experimental animals[24] there was superficial damage with irreversible yellow staining of cerebral tissue and marked depression of electrocortical activity. Epileptogenic properties were not observed.

Terramycin

Terramycin was discovered in 1949, being elaborated by *Streptomyces rimosus*. It is produced commercially by fermentation methods as a bright yellow powder. It also has a broad antibacterial spectrum which is similar to that of Aureomycin (table 1). The drug is absorbed fairly rapidly after oral ingestion and serum levels intermediate between chloramphenicol and Aureomycin are found within a few hours.[34] Terramycin diffuses into the spinal fluid slightly better than Aureomycin but less well than chloramphenicol, and spinal fluid concentrations do not always show a direct relationship with serum levels.[51] The usual oral dose for an adult is 1 gm. initially followed by 500 mg. every four hours. For children, 10 mg./kg. is given every four hours. Terramycin can be given intravenously, with a buffering agent of sodium glycinate which is easily dissolved in sterile water or normal saline and has a pH of 9. In adults 500 mg. is usually given every 12 hours. The dose for children is 250 to 500 mg. every 12 hours. The same toxic manifestations may be observed as with Aureomycin.

Terramycin cannot be given intrathecally. When the intravenous solution, even in small concentrations, was applied to the cerebral cortex of animals[24] there was a marked depression in electrocortical activity, but no epileptogenic properties were shown. There was marked damage to the smaller blood vessels with diapedesis of red blood cells and hemorrhagic discoloration of the cortex.

*Polymyxin**

The name polymyxin applies not to one substance but to a group of five closely related polypeptide antibiotics derived from various species of *Bacillus polymyxa*. It is known commercially as Aerosporin. Polymyxin A, C, and D produce such severe nephrotoxic symptoms in experimental animals that they have not been used clinically. Polymyxin B and E show much less renal toxicity and have undergone clinical trial. Polymyxin

*Polymyxin B sulfate 10,000 units = 1 mg.

B sulfate in the form of a white crystalline powder is the most available of these preparations and is the drug which will be referred to hereafter.

This drug is bacteriocidal and is the most potent antibiotic available for many of the gram-negative bacilli, including *Pseudomonas aeruginosa* (table 1). In order to gain significant blood serum concentrations this antibiotic must be given by intramuscular injection in doses of 2.5 mg./kg. per day, with a maximum dose of 200 mg. per day for an adult, given in four equally divided doses. Local pain at the injection site, malaise, pyrexia, and paresthesias may occur after intramuscular injection.[52] Mild proteinuria may occur but is usually transient. Of course, the drug should not be given to patients with preexisting renal damage.

Polymyxin B does not cross the blood brain barrier and intrathecal administration is necessary. Both experimentally[9] and clinically[53] this drug produces a pleocytosis and is capable of causing meningeal irritation. When applied directly to the cortex of cats,[24] polymyxin B caused depression of cortical activity but showed no evidence of epileptogenic properties, and the cortex appeared normal even several hours after continuous exposure.

Adequate cerebrospinal fluid levels can be maintained when the following intrathecal dosage is used: for children under 2 years of age, 2 mg. daily for 3 to 4 days followed by 2.5 mg. every other day; for children over two years of age and adults, 5 mg. daily for 3 to 4 days and then 5 mg. every other day.

Because of the nephrotoxic properties which may follow intramuscular injection of polymyxin B and the necessity of repeated intrathecal injections, this drug at present should only be used in cases of meningitis due to pyocyaneus organisms.

Neomycin

This antibiotic is derived from *Streptomyces fradiae* and is available as neomycin sulfate, a white powder which is extremely stable. The drug is bacteriocidal for a large number of gram-positive and negative organisms.[54] Its ototoxic and nephrotoxic effects preclude its administration as anything but a topical agent. When applied directly to the cerebral cortex of experimental animals[24] it produced electrographic spikes and convulsions. It, therefore, has no use in the clinical treatment of purulent meningitis.

Erythromycin

This is one of the newest of the antibiotics and is also obtained from one of the actinomycetes, *Streptomyces erythreus*. It is also known as Iliotycin. It is effective against many of the gram-positive organisms, especially the corynebacteria. *Hemophilus pertussis* is the only gram-negative organism that is susceptible. Streptococci and staphylococci which have been found resistant to penicillin, chloramphenicol, Aureomycin, or Terramycin have proved sensitive to erythromycin.[55]

Adequate blood levels have been maintained with oral administration of 20 to 25 mg./kg. daily. In adults the usual oral dosage has been 0.4 or 0.5 gm. every six hours. Occasionally nausea and vomiting occur and require a reduction in dosage to 0.3 gm. every six hours. This is the lowest dose that will maintain satisfactory serum levels. No serious toxic signs have been found.

Erythromycin does not diffuse readily into the cerebrospinal fluid in patients with normal meninges.[56] One case of staphylococcal meningitis has been successfully treated by orally administered erythromycin.[57] It has not been given intrathecally. When the powder was applied to the cortex of experimental ani-

mals[24] random spikes were produced, but seizures were not observed.

CHOICE OF THERAPEUTIC AGENTS

These nine antibiotics together with the sulfonamides afford the clinician a wide choice in therapeutic agents. In order to treat a specific case of purulent meningitis intelligently, effectively, and safely, the drugs to be used and the routes of administration must be chosen with certain factors in mind.

The prevention of bacterial resistance is extremely important. Every species of bacteria studied has been shown capable of developing a certain degree of resistance to each of the antibacterial agents. Two general patterns of the emergence of resistance have been described;[58] one is known as the penicillin pattern, and the other as the streptomycin pattern. In the treatment of a bacterial strain initially sensitive to penicillin, a single mutational step will result in an organism only slightly less sensitive to penicillin. A really high degree of resistance can only occur by the accumulation of a number of mutational steps. However, large enough doses of penicillin from the very beginning of therapy can prevent the first step mutants from surviving if the infecting organisms have not been previously exposed to penicillin. On the other hand, in the streptomycin pattern, a single mutational step can produce an organism with either a low or a very high degree of resistance. If a highly resistant mutant develops quickly, it will survive and continue to breed true to form actually thriving on concentrations of the drug as high as 1,000 microg./cc., while the remainder of the colony will be eliminated. It is for this reason that an antibiotic which produces the streptomycin resistance pattern can never be given in high enough dosage to prevent emergence of resistance.

Spontaneously occurring mutants resistant to one antibiotic may be sensitive to another, indicating different mechanisms of action of the antibacterial agents. For the gram-positive organisms, penicillin has a mode of action which differs from sulfadiazine, bacitracin, chloramphenicol, Aureomycin, and Terramycin. The combination, therefore, of penicillin plus any one of the latter group of drugs can prevent emergence of resistance of a strain which initially was sensitive to both agents.[40] The complementary therapeutic agents for streptomycin are sulfadiazine, chloramphenicol, polymyxin, Aureomycin, and Terramycin, and one of the latter drugs should be combined with streptomycin in order to prevent bacterial resistance. Chloramphenicol brings out the penicillin pattern of resistance in bacteria and should be used with such complementary agents as sulfadiazine, streptomycin, or polymyxin.

During the past three years, Gunnison, Jawitz and co-workers[59–62] have warned against combining a bacteriocidal antibiotic with a bacteriostatic agent, stating that the bacteriocidal action would be delayed. These conclusions were based on in vitro and in vivo experiments using penicillin or streptomycin and chloramphenicol, Aureomycin, or Terramycin against hemolytic streptococci. The death rate of infected mice was higher when penicillin and chloramphenicol were combined as compared to the use of penicillin alone. In these experiments, however, only single injections of these drugs were used and the serum concentrations were relatively low. It was shown by the same investigators[61] that this antibiotic antagonism could not be demonstrated when the organisms were exposed to even a low concentration of penicillin for one hour prior to the administration of the second agent. Furthermore, when penicillin and chloramphenicol were used together in sufficient dosage to insure adequate body fluid levels over a period of several days, such antagonism could not be demonstrated

by Ahern and co-workers[63] in experimental infections. Dowling and co-workers[64] found an equal amount of antagonism and synergism between penicillin and Aureomycin in experimental pneumococcal infections.

From a clinical point of view, two reports have appeared suggesting that antibiotic antagonism may have influenced the results of treatment in meningitis. Lepper and Dowling[65] found a 21 per cent fatality rate in 14 patients with pneumococcic meningitis treated with penicillin, compared to a 79 per cent fatality rate in alternate patients who were given the same dose of penicillin plus Aureomycin. Lepper and co-workers[66] noted that patients with meningitis due to *H. influenzae* recovered less quickly when treated with Aureomycin, streptomycin, and sulfisoxazole as compared with those receiving Aureomycin alone. Alexander[40] has recently evaluated this problem and has concluded that clinically one need not hesitate to combine penicillin with chloramphenicol or one of the other bacteriostatic agents. In order to prevent any hypothetical slowing of the bacteriocidal effect of penicillin, this drug should be given a few hours before starting the second agent.

TREATMENT

The following is a brief outline of what seems to be the most generally accepted method of management in each of the seven most common types of purulent meningitis. Mixed infections occasionally occur but are not discussed in detail. Their treatment is usually a matter of combining the drugs which would have been used against each of the infecting organisms.

Meningococcic Meningitis

Most clinicians[17,18,40] rely primarily upon sulfonamide therapy in this form of meningitis. Sulfadiazine remains the drug of choice although good results have been obtained with sulfathiazole, Sulfamerizine, and more recently, Gantrisin. In adults the initial dose usually given is 5 gm. of sodium sulfadiazine intravenously in 1,000 cc. of 1/6 molar sodium lactate or isotonic saline solution, followed by 1 gm. every four hours. Infants are usually given the drug subcutaneously for the first 24 hours, receiving 100 mg./kg. every 12 hours for two doses. Thereafter oral administration is continued giving 33 mg./kg. every four hours. Older children receive about one-half this dosage. Maintenance dosage is regulated to insure a blood level of 10 to 15 mg. per 100 cc.; blood samples should be drawn approximately two hours prior to the next dose of sulfadiazine. Adequate fluid intake remains important, and the accompanying use of sodium bicarbonate is still favored.

While penicillin is considered of secondary importance in the treatment of meningococcic meningitis, most clinicians[67] still prescribe it in higher doses varying from 1 to 2 million units daily. The intrathecal use of penicillin has been discarded in all but the most desperate cases. Chloramphenicol has proved effective in this type of meningitis, but the results with sulfadiazine and penicillin are so satisfactory (table 2) that a great deal more work is needed before one should consider substituting or even adding chloramphenicol to the program.

The possibility of a fulminating meningococcic septicemia with massive adrenal hemorrhages and cardiovascular collapse must be borne in mind; this would require additional supportive measures such as the use of adrenal cortical extract. The latter drug has been given in doses of 75 to 100 mg. daily for three days.

Sulfadiazine and penicillin therapy is usually necessary for five to nine days.

Hemophilus Influenzae Meningitis

This previously fatal disease has been gradually brought under control since the development of sulfonamides and the antibiotics. It is predominantly a disease of infancy and early childhood. Until two or three years ago treatment was based on sulfadiazine, specific rabbit serum, and streptomycin[68,69] given intramuscularly and intrathecally. This type of meningitis has been treated successfully with Aureomycin,[49] Terramycin, and polymyxin B,[9] but it has recently been shown that chloramphenicol[42,43] is the drug of choice since with its use the mortality rate has been reduced to less than 20 per cent. For infants and children an initial dose of 750 mg. is given orally, followed by 250 mg. every four hours. If vomiting occurs a supplemental rectal dose of 500 mg. may be given. In adults, 1 to 2 gm. is given orally as an initial dose, with 750 mg. given every four hours as a maintenance dose. The marked susceptibility of *H. influenzae* to chloramphenicol and the absence of development of resistant mutants has led to rapid elimination of the organisms, the spinal fluid usually being sterilized within 24 hours. It seems unlikely that intrathecal chloramphenicol will prove necessary. Most clinicians prefer to combine sulfadiazine in full doses with chloramphenicol (table 2). Treatment is usually necesasry for about one week.

Pneumococcal Meningitis

In spite of recent advances the mortality rate from pneumococcal meningitis remains high, averaging 30 to 50 per cent. Applebaum and co-workers[15] have reported a mortality rate of 27 per cent in a series of 125 cases. They used sulfadiazine and penicillin. The latter drug was given in relatively low doses of 400,000 to 800,000 units daily intramuscularly, as well as in high doses of 25,000 to 100,000 units intrathecally for three to five days. Nine patients developed complications from the intrathecal therapy, and death resulted in three of them. Although Dowling and co-workers[6] have shown that satisfactory spinal fluid levels can be maintained by massive intramuscular doses of penicillin, their mortality rate in a series of only 21 patients was 38 per cent. No series of cases has been reported in which chloramphenicol has been used.

At the present time, the consensus seems to be that cases of pneumococcal meningitis should receive sulfonamides, penicillin, and chloramphenicol (table 2). Sulfadiazine should be given in doses that will maintain a blood level of at least 15 mg. per cent. Penicillin is recommended in high doses of 1 million units intramuscularly every two hours. The first penicillin injection may be given intravenously over three to four hours if the patient is moribund. At least one intrathecal injection of penicillin should be given, 5,000 units in infants, 10,000 units in children over two years, and 20,000 units in adults. A second intrathecal injection may be necessary if the patient does not show definite clinical improvement. Chloramphenicol in full doses should be started about three hours after penicillin therapy has been initiated. If penicillin resistance is found to be present, intrathecal bacitracin may be necessary.

Streptococcal Meningitis

Penicillin remains the antibiotic of choice in these infections and is given with sulfadiazine (table 2). Large doses of penicillin should be given intramuscularly,[40] a total of 12 million units daily for three days and then 2 to 3 million units daily for approximately four days. Since it requires eight to 12 hours for optimal spinal fluid concentrations to be reached, at least one intrathecal injection of penicillin should be made. Although most streptococci are more sensi-

TABLE 2
OPTIMUM THERAPEUTIC MANAGEMENT OF THE COMMON FORMS OF PURULENT MENINGITIS

Causative organism	*Therapeutic agents*	*Route*
N. meningitidis	sulfadiazine	intravenous or subcutaneous and oral
	penicillin	intramuscular
H. influenzae	chloramphenicol	oral
	sulfadiazine	oral
D. pneumoniae	penicillin	intramuscular and intrathecal
	chloramphenicol	oral
	sulfadiazine	oral
Strept. pyogenes	penicillin	intramuscular and intrathecal
	chloramphenicol	oral
	sulfadiazine	oral
Staph. pyogenes	penicillin	intramuscular and intrathecal
	chloramphenicol	oral
	sulfadiazine	oral
E. coli	streptomycin	intramuscular and intrathecal
	chloramphenicol	oral
	sulfadiazine	oral
Ps. aeruginosa	polymyxin B	intramuscular and intrathecal
	streptomycin	intramuscular and intrathecal

tive to Aureomycin and Terramycin than chloramphenicol in vitro, the latter drug is usually recommended because of its ability to reach the cerebrospinal fluid more quickly and to be maintained in higher concentration than the other two antibiotics. Chloramphenicol should be started in full doses approximately three hours after the initial dose of penicillin. Should the particular strain of streptococci prove to be penicillin resistant, as determined by sensitivity tests within the first 48 hours, the alternate use of streptomycin or bacitracin may be indicated. Bacitracin should be given intrathecally daily, and only used intramuscularly if it is the only drug to which the organisms are sensitive. In some strains, the organisms may be extremely sensitive to Aureomycin or Terramycin and may be sensitive to chloramphenicol only in concentrations above 10 microg./cc. In this case either Aureomycin or Terramycin should be used in place of chloramphenicol.

Staphylococcal Meningitis

The same drugs and doses are recommended in the treatment of a staphylococcus meningitis as in streptococcal and pneumococcal types – penicillin, sulfadiazine, and chloramphenicol (table 2). Because of the higher incidence of resistant strains and the longer period of exposure to antibiotic drugs needed to insure complete elimination, this form of meningitis usually requires several days of intrathecal penicillin therapy. Most clinicians advise at least four daily intrathecal injections of up to 20,000 units in adults. If the organisms are found to be penicillin resistant but bacitracin sensitive, the latter drug should be employed at least by the intrathecal route.[31,32] Cerebrospinal fluid levels of chloramphenicol of 40 to 50 microg./cc. can be safely maintained by daily intrathecal injections of 1 to 2 mg. and have proved effective in the treatment of penicillin resistant staphylococcal meningitis.[33]

Eschericia Coli Meningitis

E. coli meningitis is more often observed in early childhood and has been described in newborn infants. The recommended therapy consists of streptomycin, sulfadiazine, and chloramphenicol (table 2). Streptomycin should be given both intramuscularly and intrathecally. In those cases in which a clear flow of spinal fluid is not obtained or in which it is extremely purulent, streptomycin should be injected intraventricularly for a few days in doses of 25 to 50 mg. Sulfadiazine blood levels should be maintained at 10 to 15 mg. per cent. Full doses of chloramphenicol should be employed. The use of this drug intrathecally or intraventricularly may be found to be the treatment of choice in the future. *E. coli* organisms are more sensitive to polymyxin B than to any other antibiotic and, in those cases in which the bacteria are or become resistant to streptomycin or in which clinical improvement fails to occur, the intrathecal administration of this drug should be considered. Streptokinase has been injected into the ventricles in cases in which the spinal fluid became extremely purulent.[70] This appeared to cause no untoward reaction, but should receive more extensive clinical trial before being recommended for general use.

Pyocyaneous Meningitis

Meningitis due to *Pseudomonas aeruginosa* is frequently caused by contamination occurring at the time of lumbar puncture even in the treatment of other forms of meningitis, or by direct extension from an infected area adjacent to the subarachnoid space. It has previously been extremely resistant to all forms of therapy. Polymyxin B[71,72] is proving to be practically a specific antibiotic for this infection and should be given by both intramuscular and intrathecal routes. Doses of 2.5 mg./kg., with a maximum dose of 200 mg., should be given daily in divided doses every four hours intramuscularly; 2.5 to 10 mg. are advised for daily intrathecal injections. Therapy may have to be continued for over one week, and the danger of relapse should be carefully considered.

Streptomycin should be given intramuscularly, and most clinicians usually advise at least one intrathecal injection as well (table 2). There is no clear indication for sulfonamide therapy and many do not recommend these drugs in this infection.

DISCUSSION

From a practical point of view, the treatment of purulent meningitis often must be started before the organism has been definitely identified and before sensitivity data are available. In a suspected case of meningitis, a diagnostic lumbar puncture should be performed immediately. If spinal fluid cannot be obtained in infants with signs of meningeal involvement, a ventricular tap should be performed. A gram stain should be done on a direct smear of either the turbid fluid or a centrifuged specimen. If gram-negative diplococci are identified, a presumptive diagnosis of meningococcal meningitis should be made and treatment started at once using sulfadiazine intravenously or subcutaneously and orally and penicillin intramuscularly. If gram-positive cocci are seen, another lumbar puncture should be done and an intrathecal injection of penicillin given. Penicillin should also be started intramuscularly in high doses. Sulfonamides should be started by mouth, and three hours after the onset of penicillin therapy chloramphenicol should be started. If gram-negative bacilli are found, streptomycin should be given intramuscularly and intrathecally and sulfadiazine and chloramphenicol by mouth. In a case showing all the clinical signs of active purulent meningitis but in whose spinal

fluid no organisms can be definitely identified, penicillin should be started intramuscularly and sulfadiazine and chloramphenicol given by mouth. Very often such cases prove to be due to *H. influenzae*, the small gram-negative rods being sometimes difficult to find on poorly smeared or stained preparations.

Most hospital facilities will provide a bacteriologic diagnosis in 12 to 24 hours, but in most instances it is 36 to 48 hours before complete sensitivity tests have been performed. Therefore, a change in the plan of therapy may be made 12 to 48 hours after it has been started, selecting the combination of drugs and the routes of administration that are most likely to provide the safest and most rapid elimination of the infecting organisms.

In a sense, purulent meningitis is never primary, but occurs when organisms reach the subarachnoid space from other regions of the body. Spread is usually hematogenesis resulting from a transient bacteremia secondary to infection in the oral-pharyngeal-nasal area or from the respiratory or gastrointestinal tract. Direct extension from paranasal sinus, middle ear, or mastoid infection is another cause, and results more commonly in pneumococcal, streptococcal, and staphylococcal meningitis. Compound skull and spinal column injuries are capable of producing meningitis but the incidence has been greatly reduced by proper surgical management and the prophylactic use of antibiotics. Patients with basal skull fracture involving the paranasal sinuses or middle ear leading to rhinorrhea or otorrhea may escape cerebrospinal fluid infection during the initial posttraumatic period only to return in months or years with purulent meningitis on the basis of a persistent cerebrospinal fluid fistula. Postoperative craniotomy and laminectomy infection account for a small number of cases of meningitis.

In addition to the treatment of meningitis, one must always be aware of the possibility of a localized sinus or ear infection or a cerebral or cerebellar abscess which will require surgical therapy, as well as a cerebrospinal fluid fistula which may later need to be repaired.

During the past three years several reports[73–75] have drawn attention to the relatively high incidence of subdural effusions as a complication of purulent meningitis in infancy. These fluid collections show the same xanthochromia and high protein content as seen in the chronic subdural hematomata of traumatic origin in infants. The fluid may or may not be infected. Persistent fever, irritability, vomiting, or a tense fontanelle in a baby who has shown initial clinical improvement after the start of antibiotic therapy, and in whom the spinal fluid has shown signs of clearing, should lead one to suspect the presence of subdural fluid collections. Most clinicians favor diagnostic subdural taps with frequent aspiration. Many cases will respond to this simple form of treatment. McKay and co-workers[73] favor operative intervention with removal of the subdural fluid and membranes if conservative measures fail.

Patients with purulent meningitis are usually critically ill and require more in therapy than proper antibiotic medication. Attention must be given to fluid and electrolyte balance in patients who may be vomiting and receiving sulfonamides. Nutrition may have to be maintained by gavage or intravenous routes during the early period. Many workers favor the prophylactic use of anticonvulsants, giving phenobarbital in relatively small doses. Occasionally stronger sedation is indicated for extreme restlessness or delirium; paraldehyde has proved an effective and safe drug for this purpose, usually being given rectally or intramuscularly. Morphine and similar hypnotics should be avoided. Blood

transfusions are occasionally indicated as a supportive measure or to correct an existing anemia. Hyperthermia should be controlled by alcohol sponges, fans, coolers, and so on. Oxygen therapy is frequently a useful adjunct in severe infections.

SUMMARY

In summary, there are a number of principles which should be followed if the optimum results in the treatment of purulent meningitis are to be achieved and if disabling sequelae are to be reduced to a minimum:

1. Early diagnosis of the infection, both clinical and bacteriologic.
2. Proper choice of antibiotic agents.
3. Prompt institution of therapy, rapidly achieving and maintaining high serum and cerebrospinal fluid levels of two complementary acting antibiotics.
4. Avoidance, when possible, of dangerous drugs and unnecessary intrathecal injections which may be injurious to the patient.
5. Elimination of focal suppurative lesions.
6. Early recognition of possible complications, such as subdural effusions, relapse of infection, or development of hydrocephalus.
7. Supervision of the total needs of a patient critically ill with purulent meningitis.

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We may therefore conclude, with Hughlings Jackson, that the teaching of pathology, if inconclusive alone, is right in its indications, and that, in at least a large number of epileptic attacks, the process of the fit commences in the cerebral hemispheres. The convulsion thus reached derives additional strength from the experimental demonstrations, already referred to, that epileptiform convulsions may be excited by irritation of the motor region of the cortex, and also from the case of epilepsy recorded by Oebeke in which the convulsions were arrested on one side by a lesion in the central ganglia of the opposite hemisphere. It is exceedingly probable that the attacks which begin deliberately commence in those cortical centres, which have been proved to possess functions the disturbance of which constitutes the first symptoms of the attack; and our present knowledge of the physiology of the brain makes it almost certain that this is the case when the warning of the attack is of such high specialization as to indicate a psychical process. In cases in which the initial symptoms are less elaborate, spasm or "crude" sensation, we cannot at present exclude altogether the central ganglia as the possible seat of the discharge.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

CLINICAL PATHOLOGIC CONFERENCE

Raymond D. Adams, M.D.
Section Editor

Presented by Miller Fisher, M.D.

CLINICAL SUMMARY

A 58 year old professional man was in good health until March 4, 1953 when, while buying a ticket in a railroad depot, he suddenly fell down unconscious. He was in the company of a physician who thought the patient had collapsed due to myocardial infarction, but the pulse was of normal rhythm and not unusually rapid. There were no convulsive movements. Loss of consciousness lasted approximately ten minutes and then a clearcut dysphasia became apparent. The patient was rushed to the hospital, but when an electrocardiogram proved normal he was taken home. The dysphasia gradually cleared over a period of two hours, and except for some anxiety the patient was quite normal the rest of the day. There had been no paralysis or headache. The next ten days were uneventful, but then brief attacks of dizziness appeared occurring one to five times a day. The patient usually sat down, rested his head on his arms, and in one or two minutes pronounced the attack finished. There was no rotatory feeling but rather a peculiar sensation in the head. Following at least one attack definite aphasia, chiefly nominal, occurred for about five minutes. After these episodes had persisted for about two weeks, the patient was hospitalized on March 29.

The only additional history included an uncomplicated cholecystectomy and infectious mononucleosis in 1949. General and neurologic examinations were not significantly abnormal. The pupils were equal and reacted well to light. Fundi were not remarkable. Visual fields were full. There was no nystagmus. Ocular movements were full. There was no facial weakness. Hearing was normal. Throat and tongue were normal. Motor power, coordination, finger-nose and heel-knee tests, and sensation for pin, vibration, touch, and position were not remarkable. The patient's mind and memory were intact. Blood pressure was between 160/100 and 150/90. The blood Wassermann test was negative, sedimentation rate, 6. The blood count and urinalysis showed no abnormality. An electrocardiogram was suggestive of mild myocardial abnormality. Roentgenograms of the chest and skull were normal, the pineal gland lying in the midline. An electroencephalogram was entirely normal. Liver function studies and blood chemistry including sugar and urea nitrogen were normal. An exact diagnosis could not be reached and the patient was discharged with instructions to rest.

During two months of rest (April and May) he was quite symptom-free and in June returned to his office. Soon it became apparent to his wife and co-workers that he had difficulty in naming objects and people. His memory became progressively impaired and he used notes as reminders. His wife noticed an unusual verbosity in that he harangued his clients at great length, quite unlike his usual manner. On the other hand, casual acquaintances noticed nothing amiss. The patient's usual energy was preserved and he continued to work. About

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the beginning of July, trembling and mild weakness of the right hand appeared, followed in a few days by dragging of the right leg. Propositional speech became progressively impaired although he could still converse readily. On July 14 his condition deteriorated rather abruptly with great weakness of the right side of the body and accompanying drowsiness. The next day he could walk only with difficulty. There had been no incontinence, headache, or convulsion. He had continued to eat well.

At this time examination showed a well-developed, well-nourished man lying quietly in bed. Spontaneous and responsive speech were almost absent and the patient seemed to comprehend nothing. There was a slight tendency to weariness, but he was wide awake and usually just gazed at the examiner when asked to put out his tongue, close the eyes, and so on. Any attempt at answering questions—"How are you?", "Do you have pain?"—soon became puzzled jargon. He did not name the simplest of objects.

The pupils were equal and reacted to light. There was no nystagmus and ocular movements were full. The fundi including disks, retina, and vessels were not remarkable. The visual fields were difficult to assess but no hemianopsia could be demonstrated. There was clearcut weakness of the right lower face. Hearing was good and the ear drums normal. Motor power in the right upper and lower limbs was 30 to 40 per cent of normal. A conspicuous abnormality was the presence of a rhythmic, flexion-extensor tremor of the fingers and of the toes and foot on the right side. The tremor was regular at approximately four per second. The face was not involved. The tendon reflexes were brisk and approximately equal on the two sides. There seemed to be a cogwheel type of rigidity in the right limbs. The plantar response was extensor on the right, flexor on the left. Sensation could not be adequately tested, but withdrawal from pinprick was more prompt on the left. The patient could walk by himself only with great difficulty owing to the weakness of the right leg. There was no incontinence or neck stiffness. Temperature, pulse, and respiration were normal. The heart and lungs were not remarkable. Blood pressure was 160/100. Peripheral pulsations were present in both internal carotids, both anterior tibials, but only in the left posterior tibial artery.

Arrangements were made to transfer the patient to a hospital in a neighboring city, but during the night of July 17 he became comatose and died.

DISCUSSION

At the time of the patient's hospital admission one month after onset of his illness, it was thought that cerebral vascular disease was probably responsible for his symptoms. Sudden fainting spells are not at all rare in older people who are quite well otherwise. Such attacks are commonly akinetic, convulsive movements not being part of the picture. The pathologic or pathophysiologic basis for such episodes is unknown, but cerebral arteriosclerosis is often held responsible. To have dysphasia follow such episodes is rare and some other category of attack has to be considered. In the case at hand, the sudden onset, unconsciousness, temporary dysphasia, lack of convulsive movements, the age of the patient, and the presence of mild arterial hypertension pointed strongly to vascular insult. When mild attacks of dizziness appeared, followed at least once by dysphasia, the picture was reminiscent of the transient episodes which often herald the onset of a stroke due to cerebral thrombosis. The negative medical and neurologic examinations bore out this clinical impression, which was further substantiated when rest for two months resulted in complete relief of symptoms.

When the patient was hospitalized it was also suggested that he was having transient attacks of cerebral ischemia due to temporary cardiac dysfunction. Such an interpretation is often favored by cardiologists in similar cases but, in the absence of evident cardiac disease, the Stokes-Adams syndrome is, for practical purposes, the only type of cardiac disorder likely to lead to recurrent cerebral disturbances. The heart is probably much too quickly blamed for atypical vertigo, faintness, or attacks of so-called cerebral vasospasm, when a careful

analysis of the patient's complaints will usually suffice to indicate the true nature of the symptoms.

After two months free of symptoms, there occurred gradually a progressive deterioration, characterized in order of appearance by nominal aphasia, memory loss, weakness of right arm and leg, drowsiness, complete aphasia, and death. The patient's relatives, although not certain, thought that these deficits appeared insidiously (until the last few days when deterioration was rapid) and had not advanced in an abrupt stuttering fashion. If this information was correct the diagnosis of incipient cerebral thrombosis would have to be revised. Cerebral thrombosis practically never produces a slowly progressive decline, but tends rather to lead to episodic, abrupt worsenings, fractions of the total hemiplegia being added from time to time. This is true also of thrombosis of the internal carotid artery, and in this case pulsation in both carotid systems was good. Rarely, an intracerebral hemorrhage leads to increasing deficit over a period of a month or more, but usually headache is present.

If the relatives' story was reliable, the slow, progressive course would point to an expanding intracranial lesion, particularly a tumor either primary or secondary. Yet at no time was there headache; papilledema was absent the day before death, and previous roentgenograms of the skull and an electroencephalogram were normal. Furthermore, the onset of illness with a sudden attack of unconsciousness followed by spells of dizziness did not suggest tumor. In regard to secondary tumor, there was no weight loss, the sedimentation rate was normal, and a roentgenogram of the chest showed no lesion. Secondary tumor deposits in the brain rarely run their course without the appearance of pulmonary lesions, but a film of the chest had not been made in the weeks prior to death. An intracranial abscess occasionally occurs unexpectedly without any source and unassociated with signs of meningeal irritation, but in this case the illness had been too lengthy. The presence of a subdural hematoma had to be kept in mind, although the slow, progressive type will not lead to total aphasia without marked disturbance of consciousness. There was no history of injury to the head but, of course, this is not significant. The abrupt onset of the first symptoms and the lack of headache would be atypical of a subdural hematoma.

The presence of the rhythmic, four per second tremor of the right hand and foot was most striking, but unfortunately no one who was consulted was aware of any diagnostic value attached to such a sign. The tremor was clearly not that of partial continual epilepsy but mimicked the trembling of parkinsonism, except for its slightly faster rate. The fingers and toes seemed to flex synchronously and all five digits of the hand were involved.

Finally, the diagnosis of suspected brain tumor was made. In this conclusion, the character of the onset, the period of cessation of symptoms, and the absence of headache and papilledema were disregarded, in view of the slow, progressive final course which is scarcely ever due to vascular disease.

PATHOLOGIC FINDINGS

The left temporal lobe, from its anterior tip to a point 7 cm. posterior was occupied or replaced by a huge tumor mass, which histologically was of the glioblastoma multiforme type. A large uncal herniation on the left side was associated with multiple pontine hemorrhages. In its deeper portion the tumor clearly invaded the inferolateral portion of the putamen and adjacent internal capsule.

COMMENT

This case is an example of an extensive tumor running its entire course without headache or papilledema. The interpretation of the progressive course as suggestive of tumor rather than arterial disease proved correct. Pathogenesis of the initial attack remains obscure, but the attacks of dizziness probably were minor seizures. The failure of the electroencephalogram to show an abnormality provides another example of the fact that as a rule clinical data must still provide the essential ingredients of a correct diagnosis. The nature of the rhythmic tremor of the paretic limbs remains obscure, but since it is most unusual for vascular disease to produce such a picture, it is possible that the presence of a tremor might be indicative of tumor.

The most common form (of minor attack) is transient loss of consciousness without conspicuous convulsion. A patient suddenly stops for a moment in whatever he or she is doing, very often turns pale, may drop whatever is in the hand, and then is better. There may be no visible spasm, or there may be a slight stoop forward, or a slight quivering of the eyelids. The patient may or may not fall. Pallor of face is by no means invariable; I have watched many such attacks in which there was not, from first to last, the least change of color in the face. In some of the cases in which pallor does occur, the change of color is not always general. The cheeks may not change color at all, although the lips and the skin around become strikingly pale. There is rarely any cyanotic tint. Sometimes, as an attack is passing away, the face becomes flushed, and this whether there has or has not been any initial pallor. The attack usually lasts only a few seconds. The return of consciousness may be sudden, and the patient, after the momentary lapse, may be in just the same state as before the attack, may even continue a sentence or action which was commenced before it came on, and suspended during its occurrence. Very often, however, the patient is left in a more or less confused state, which slowly passes away. When full consciousness is suddenly regained, although it had been for a second or two completely lost, the patient may not know of the occurrence of the attack, and only become aware of it by finding that persons are looking at him with surprise. In many cases, however, some warning sensation precedes the loss of consciousness, and of this only the patient is conscious, and it is for this reason that the attacks are often termed "sensations." This warning may be the same as that which, in the same case, precedes the major attacks, but in many patients there is no such correspondence. Usually the sensation of which the patient can give an account is merely the aura preceding an actual loss of consciousness. To the patient the former, to the friends the latter, constitutes the evidence of the attack. In rare instances in which consciousness is not lost, the sensation experienced by the patient constitutes the only symptom of the attack.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

NEWSLETTER

APRIL, 1954

Howard D. Fabing, President
Walter O. Klingman, President-Elect
Francis M. Forster, Vice-President
Alexander T. Ross, Secretary
Dave B. Ruskin, Treasurer

AMERICAN ACADEMY OF NEUROLOGY

Epilepsy League Meeting Outlined The annual meeting of the American League Against Epilepsy, to be held at the Shoreham Hotel, Washington, D. C., will begin with a joint session with the American Academy of Neurology on Saturday, May 1, and continue through noon Sunday, May 2. Included in the joint session will be an open discussion of a progress report of the Legislative Committee of the League to be presented by Roscoe L. Barrow, dean of the College of Law at the University of Cincinnati.... The scientific sessions will include papers ranging from basic laboratory research to the use of newer diagnostic technics and drugs, and the social and employment aspects of epilepsy. Highlighted among the latter are a study of the accident rates of epileptics by Harry Sands and a progress report of the Gallup survey of public attitudes toward epilepsy by William Caveness.... A cocktail party will be held from 5:00 to 7:00 p.m., Saturday, May 1, in the Louis Seize Room of the Shoreham; Academy members and their guests are cordially invited. ... Ben H. Gray, director of the National Epilepsy League, will address the Woman's Auxiliary.

ANA To Meet In Atlantic City The Seventy-Ninth Annual Meeting of the American Neurological Association will be held at the Hotel Claridge in Atlantic City (June 14-16). The scientific sessions are scheduled for the morning, afternoon, and evening of Monday, June 14, morning and afternoon on June 15, and a morning session only on June 16. On Tuesday evening, June 15, the annual banquet will be held. President of the ANA is Roland P. Mackay, and secretary-treasurer, H. Houston Merritt.... Prior to the ANA meeting, the American Association of Neuropathologists will convene on Sunday, June 13, at the Hotel Claridge.

New MS Clinic Opened in Washington Opening ceremonies of the Multiple Sclerosis Center at George Washington University Hospital were held on February 15, under the chairmanship of Walter Freeman, who heads the Medical Advisory Board of the Washington Multiple Sclerosis Society. The objectives of the new center are essentially diagnostic and investigative. During the ceremonies, a key,

symbolizing the Society's purpose to unlock the mystery of multiple sclerosis, was presented by District Commissioner Renah Camalier to Dr. Walter A. Bloedorn, dean of George Washington University Medical School.... Mr. Marshall Hornblower is chairman of the Washington Multiple Sclerosis Society.

Spanish Institute on Neurology at Barcelona An Institute on Neurology at the Holy Cross and St. Paul Hospital (Hospital de la Santa Cruz Y S. Pablo), Barcelona, began its courses on March 10 and will continue until June 2. The scientific sessions of this neurologic institute, under Prof. L. Barraquer Ferre, comprise clinical conferences and reports on many of the major disease areas and problems in modern neurology.... Secretary and in charge of the sessions is Dr. L. Barraquer-Bordas, Lauria 102, Barcelona.

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Brown Comments On British Neurology An important phase in Joe R. Brown's neurologic peripatetics abroad last summer (see Newsletter, February, 1954), was his visit to the British Isles. Particularly provocative was his tour of a unit of the Institute of Neurology at the National Hospital, Queen Square, London. Here he was impressed by a teaching session under Dr. S. P. Meadows, and making rounds with Doctors E. Arnold Carmichael, J. St. C. Elkington, and Sir Charles Symonds. He also was intrigued by current studies in hemispherectomies on children with hemiparesis, epilepsy, and behavior disorders, (a subject of major interest to Dr. Carmichael).... On the visit, JRB reports certain differences in English and American clinical neurology. "It appears in England that more attention is paid to a formal study of muscle tone and perhaps less attention to the sensory examination - - - The history taking seems to reflect variation in the cultural setting of the English patient as compared with the midwestern American patient - - - I gained the impression that the rehabilitation of the chronic neurologic patient had not attained the same interest it has in some areas of the U.S.A."... The teaching at Queen Square, according to JRB, is directed to graduate students who wish to specialize in neurology or improve their neurologic acumen for general medical practice. After examining neuropathologic specimens shown by Dr. Mair and being guided through the Institute's active department of neuroradiology by Dr. Bull, JRB still had an opportunity to thumb through the new book on the parietal lobe by Dr. Macdonald Critchley, dean of the Institute of Neurology, before departing for his visit to Sir Russell Brain at the London Hospital. Here he observed interesting clinical cases and a revealing motion picture of a patient with an unusual type of convulsive disorder.... From London, JRB proceeded to Oxford to see Dr. Ritchie Russell, who

graciously sacrificed a holiday to discuss neurology at the Radcliffe Infirmary. Dr. Russell's special interests lie in clinical research, the care of acute poliomyelitis, and the rehabilitation of the disabled neurologic patient. He likes to train neurologists in clinical research and is currently interested in cervical cord changes with progressive paraplegia secondary to hypertrophic bony ridges (cervical spondylosis).... Next on JRB's itinerary was Edinburgh where he made rounds with Dr. Norman Dott and had an occasion to chat with Dr. Ninian Bruce who is completing his revision of the celebrated textbook on neurology of Kinnier Wilson.

* * * * * *

Conference on Nerve Regeneration at NINDB A conference on the status of research in regeneration of the central nervous system is tentatively scheduled at the National Institute of Neurological Diseases and Blindness, Bethesda, Maryland (May 7-8). The conference, which will be headed by Louis B. Flexner of the department of anatomy, University of Pennsylvania, will review progress in regeneration experiments on submammalian and mammalian tissues. An additional purpose is to explore new vistas of investigation which might lead to a productive national program in research in this field. On the program are: R. Lorente de No, Roger W. Sperry, Paul A. Weiss, William W. Chambers, Ralph Druckman, Leslie W. Freeman, Ralph W. Gerard, William F. Windle, and many other noted scientists in the field of experimental neurology.

Multiple Sclerosis Society Approves Grant Awards Dr. Harold R. Wainerdi, Medical Director of the National Multiple Sclerosis Society, announces that the Society's Medical Advisory Board recommended approval of six research grant applications in multiple sclerosis and related fields. The principal investigators of the approved grants are: Michele Gerundo, Pinckney J. Harman, Eli Robins, Albert Schatz, Harry Sobotka, and Paul Thygesen.

Muscular Dystrophy Foundation Awards Research Grant Dr. A. L. Delaney, president of the National Muscular Dystrophy Research Foundation of Liberty, Texas, announces the award of a research grant in the amount of $5,000 to the Southwest Foundation for Research and Education, San Antonio, Texas. The project is a study of individual metabolic patterns for families having a history of muscular dystrophy, and is being conducted under the supervision of biochemist Dr. Roy B. Mefferd.... D. Denny Brown is chairman of the Foundation's Research

Advisory Board. The executive offices of the foundation are at 709 Main Street, Liberty, Texas.

Anniversary of Constantin von Monakow Commemorated The Swiss Neurological Society held a special session (December 5) to commemorate the 100th anniversary of the birth of Prof. Constantin von Monakow (1853-1930). On this memorial occasion the Faculty of Medicine of Zurich University bestowed honorary doctorates to Prof. Dr. Oskar Vogt, Neustadt (Schwarzwald), for his contributions to the anatomy and pathology of the brain; to Prof. Dr. Jean Lhermitte, Paris, for his fruitful scientific work in cerebral physiology, pathology and clinical neurology; and to Dr. Macdonald Critchley, London, in recognition of his studies in the components, mechanisms, and reciprocal actions in the degeneration of the higher nerve functions.

Percival Bailey

Neurology BOOK REVIEWS

Atlas of Electroencephalography.

F. A. Gibbs, M.D. and E. L. Gibbs. Second edition. Cambridge: Addison-Wesley Publishing Company, Inc. Volume I, 1950. 320 pages. $25.00. Volume II, 1952. 420 pages. $25.00.

This stupendous reference work, published in its second edition in two volumes (with another one to come) about nine years following its first one-volume edition, contains much more theoretical and research material than before. Volume I alone comprises ten chapters and six appendices, in addition to bibliography and index. It is appropriately dedicated to Berger, the father of human electroencephalography.

Chapter 1 gives a rapid history of the subject, and describes the last years and the sad end of Berger to whom just recognition came only late. Chapter 2 describing the shape of the problem pleads for "flexibility of approach" to this complex multidimensional subject, and submits that, "what might be considered differences of opinion are often found on analysis to be differences between two points of view that complement each other." Chapters 3 and 4 on physics, chemistry, and physiology are more detailed than the earlier edition, but will not be considered by physicists, chemists, or physiologists as giving advanced material. However, the bare essentials needed by a clinical electroencephalographer, for whom this atlas has been intended, are thought to be met with.

The value of these chapters has been enhanced by description and pictorial representation of voltage measurement of single dipoles and their supposed relationship to the importance of monopolar recording of the voltage of brain waves. Since in electroencephalography one is dealing with the potentials of thousands of interconnected dipoles, which cerebral neurones are, and with their complex and integrated parameters, it would be wrong to infer from the previous premise that bipolar recording of such potentials is unnecessary. Algebraically-summated value of voltage may be more important at times than the absolute value of voltage. Some of the controversial and dark areas concerning the intrinsic nature and origin of brain potentials are set forth. The reconciliation of varied ideas on the subject is intrinsically difficult, if not impossible, and is not seriously attempted in this book. The description of Lorento de No's work on double layers of dipoles of nerve fibers and surrounding fields of nerve action potentials is welcome. Morison and Dempsey's important contribution suggesting the role of intra-laminar nuclei of the medial thalamus in the production of spontaneous rhythm of the whole cortex is mentioned only in passing. Elaborate description is given of the concept of energy underlying neuronal activity. Nutritional homeostasis and controlling

factors of brain waves – oxygen, carbon dioxide, etc. – are specifically described. The remaining chapters are on methodology, general characteristics of electroencephalography, what is normal, changes with age, sleep, and other conditions. Appendices cover instrumentation, artifacts, authorized specifications of machines given by the American EEG Society, laboratory organization, and operation. The general character of electroencephalography and the details of the technic of taking a routine record and its pitfalls are elaborately described. Anybody who is going into the field cannot ignore this vast amount of technical information.

Concerning technic, many workers will not agree with the statement that monopolar recording gives "all the significant information that can be obtained with bipolar recording." At least it is not true of many cases with expanding lesions. The advantages of bipolar technic in localization used by many competent electroencephalographers all over the world are minimized. Its varied forms are not even described. Also the merits of bipolar recording with short or long interelectrode distance and those of studying the same area from different perspectives (different scalp points and other reference points) not only to obtain an adequate sampling of it but also to correct for the factor of possible equipotentiality are overlooked. While in routine epilepsy studies 12 point system in monopolar set-up may be adequate, much more elaborate coverage of the head with additional leads (10 or 12 – posterior temporals, Sylvian notch, premotors, lateral parietals, etc.) and varied and elaborate but flexible electrode patterning are often needed for accurately localizing space-occupying lesions in different regions before surgery. It is hoped that this matter will be dealt with and part of the authors' early localizing system (1941) restated in Volume III.

As to interpretation, the importance of visual analysis of brain waves is rightly stressed and advantages and limitations of instrumental analysis, first done by the authors in collaboration with Grass, are set in proper perspective. Two hundred and ten actual size 8 channel retouched tracings of 10 seconds each represent a most admirable display. An illustration of the adult norm established on the basis of 1,000 normal people is useful, but it should be considered as no more than an over-simplified code to distinguish normal from abnormal. Numerous complex or mixed slow, fast, and other abnormal patterns occurring in different proportions in clinical cases with varying disturbance in amplitude, frequency, modulation, form, and distribution, are not considered in the norm diagram. When visual analysis is so much stressed the voltage, form, frequency-mixture, notching, spiking, over-modulation, amplitude stereotypy, and other variables need some consideration. Part of this difficulty is, however, offset by the many full-sized plates which illustrate some of the complexity of the pattern in both volumes. If an unwary novice undertakes to judge a normal from an abnormal electroencephalogram only from a reference book, especially from a norm diagram as some unfortunately do, he may fail to identify many minor to moderate weight signs in a tracing which are not emphasized in the norm but which should have cumulative rating in the final evaluation. He may under- or over-interpret a record.

The "bi-parietal hump" found in sensory-motor areas in first stage of sleep assumes different wave characteristics, which are not all hump-like. Reference to Liberson who first mentions this in 1945 has not been given. Nor is the proper reference made to alternate ear ground technic first mentioned in literature in 1947, later adopted by the authors and facilitated by the incorpora-

tion of an attachment in the Grass machine.

Volume II, fittingly dedicated to Dr. Lennox, deals with epilepsy in a most comprehensive manner. Few aspects of the subject are left untouched. This indeed is a notable monograph. It is strictly in line with the authors' chief interest and emphasis and contains much new material. It comprises ten chapters in addition to bibliography and index.

Incorporation of Rosenbleuth's and Cannon's work on induced seizure discharges in the chapter on neurophysiology and also recent investigations is appropriate. The concept of normal electrical oscillation based on the concept of the balancing of restoring and displacing forces in the chemical system of the brain cells is illustrated by diagrams. It is interesting but admittedly leaves many aspects of the difficult problem untouched. The concept of spread of excessive energy from a group of abnormally functioning brain cells which lock neighboring and distant cells in step in an epileptic attack as being due to the lowering of intra- and intercellular resistances and breaking down of structural barriers is certainly one of the important perspectives. However, the nature of the relationship between the quantity and quality of abnormal discharge and lowering of cellular resistances and barriers in terms of spread is altogether not clear. The same type of discharge, at least what is seen electroencephalographically, may or may not lead to explosive spread.

Extensive clinical and electroencephalographic material on over 11,000 epileptics is presented in 59 statistical tables and 50 figures. Some of it is highly valuable, in addition to some that is loosely correlated and serves no important purpose. A large number of full-plate retouched electroencephalograms are shown illustrating varieties of epileptic patterns which serve as a visual education aid.

Contrary to the custom followed in this and other earlier works by the authors, most workers are now abandoning the use of clinical terms such as petit mal, grand mal, and psychomotor to designate electroencephalographic waves. That is for the purpose of avoiding confusion, since the same patterns (e. g. bilaterally synchronous spike-and-waves, spikes, slow waves, etc.) may sometimes be seen in different forms of epilepsy and rarely in nonepileptic condition, although from the point of view of incidence, spike-and-wave is seen much more frequently in petit mal than grand mal epilepsy. The same form of epilepsy (grand mal) may be associated with different patterns (e. g. slow waves, short bilaterally synchronous spike-and-waves, spikes, etc.) in interseizure periods which even the authors recognize. Three per second spike-and-wave may be seen in the temporal lobe of a psychomotor epileptic without clinical petit mal epilepsy. Even patterns during a particular type of seizure (Jacksonian or psychomotor) may vary, too, from person to person.

As against the view of the Montreal, French, and other workers, the authors maintain that in petit mal epilepsy the thalamus plays a less important role than the cortex. Reconciliation of these opposing views lies probably in the recognition of the possibility of different degrees of synergistic or independent action of these two structures in different cases.

Significant statistical material for an electroencephalographer is given on over 678 cases of psychomotor epilepsy. Some of these cases have no abnormal motor or behavior component (automatism) but are only associated with well-known abnormal subjective changes referrable to sense modalities or ideational patterns found associated with temporal lobe focus and pathology as established by Penfield and other workers in their numerous stimulation and ablation work on

humans. They are all lumped here under the category of psychomotor epilepsy. Many persons would take exception to the term psychomotor epilepsy if applied to some of these cases that do not have any motor component in their seizures. Tentatively, "temporal lobe" seizures would be a better term under which to include all these phenomena until more is known about their exact locus or interrelated locus or origin. Anterior temporal focus is found in psychomotor cases by the authors in 30 per cent of the time in waking and in 88 per cent of the time in sleep. Other workers, in large series of similar cases, have shown a focal temporal pattern not of one kind (sharp spikes) but of different kinds 80 per cent of the time in *waking*.

Introduction of sleep study by the authors to activate inherent abnormal pattern is new and fortunate. Sleep is exclusively useful in electroencephalographic diagnosis in some cases, but often it is not any more helpful than when an adequate time for a waking record is allowed (30 minutes to one hour and a half). This does not certainly make sleep study unnecessary. If the waking record is unproductive or impracticable or only faintly helpful, focally or generally, a sleep study should be undertaken, but to omit waking for sleep study, as is the custom in some laboratories, is unjustifiable and often unnecessary. If desired, some sort of compromise program can be planned on the basis of findings in waking and balance of available time for sleep study. And this can be done when it is remembered that more often than not the first 10 to 20 minutes of sleep are probably more important than its later stages.

The specificity of 14 and 6 per second positive spikes seen in sleep as being signs of thalamic and hypothalamic epilepsy can be seriously questioned on at least two grounds. First, they are seen, according to author's own description in heterogeneous clinical conditions (see table 55, p. 330, also p. 329). Second, they have rarely been seen by others in *waking* in so-called "cortical" epilepsy.

The concluding chapters on medication and surgical ablation of seizure foci will be considered highly valuable. The lead given on the latter subject by Penfield and his colleagues has been acknowledged.

These beautifully printed and bound monographs represent an outstanding addition in the fields of electroencephalography and epilepsy and should stimulate and challenge all those who are interested in these subjects.

B. K. B.

CORRECTION

The Table of Contents of the March 1954 issue of NEUROLOGY listed erroneously the title of a paper by Dr. Hildred Schuell. The correct title is "Clinical Observations on Aphasia."

On page 244, the correct title of Dr. Bertram E. Sprofkin's paper is "Cheiralgia Paresthetica" (Wartenberg's Disease).

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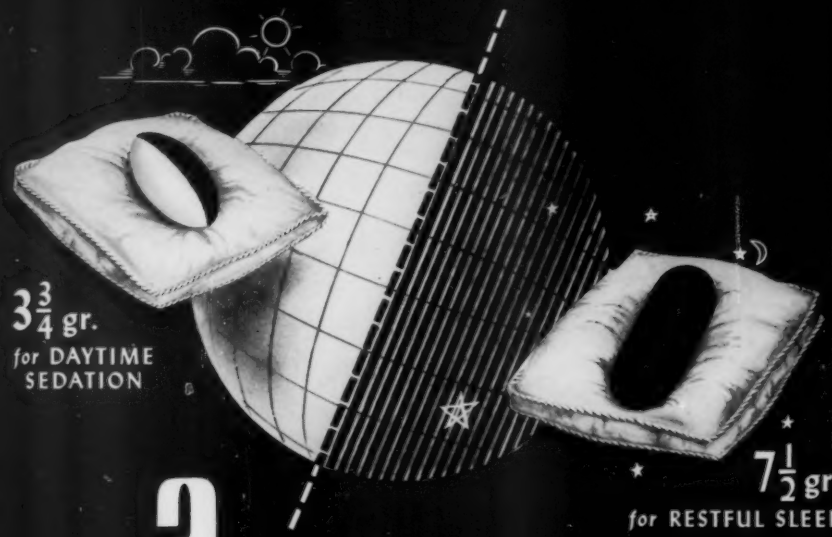

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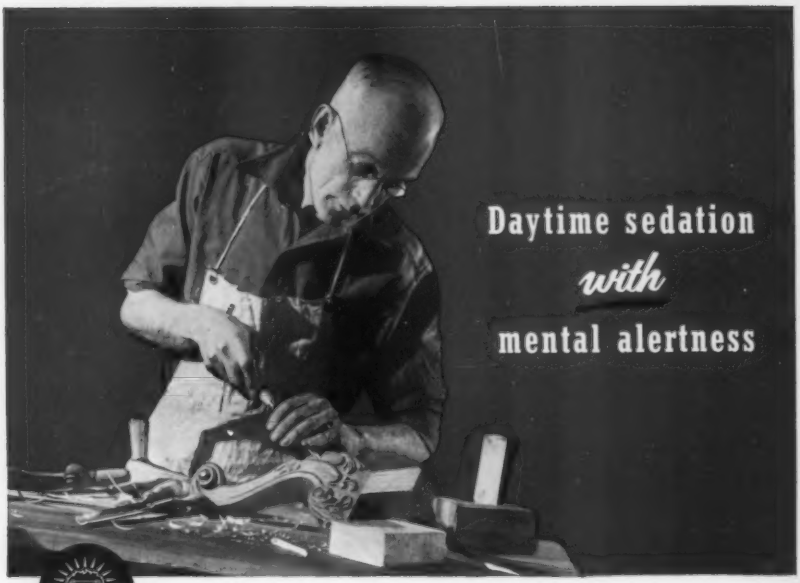

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